#### **EAST Search History**

| Ref<br>#   | Hits | Search Query                             | DBs   | Default<br>Operator | Plurals | Time Stamp        |
|------------|------|--|---|---------------------|---------|-------------------|
| S1         | 836  | "562/450",CCLS.                          | US-PGPUB;<br>USPAT;<br>USOCR                | OR                  | ON      | 2007/05/02 12:36  |
| S2         | 295  | S1 and @ad<="20020311"                   | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR                  | ON      | 2007/05/02 17:08  |
| S3         | 44   | ((PAUL) near2 (SUTTON)).INV.             | US-PGPUB;<br>USPAT;<br>USOCR                | OR                  | ON      | 2007/05/02 12:37. |
| S4         | 10   | ((RICHARD) near2<br>(VIVILECCHIA)).INV.  | US-PGPUB;<br>USPAT;<br>USOCR                | OR                  | ON      | 2007/05/02 12:38  |
| S5         | 366  | ((DAVID) near2 (PARKER)).INV.            | US-PGPUB;<br>USPAT;<br>USOCR                | OR                  | ON      | 2007/05/02 12:38  |
| S6         | 1    | ((MARILYN) near2 ("DE LA<br>CRUZ")).INV. | US-PGPUB;<br>USPAT;<br>USOCR                | OR                  | ON      | 2007/05/02 12:38  |
| <b>S</b> 7 | 1    | ("5463116").PN.                          | US-PGPUB;<br>USPAT                          | OR                  | OFF     | 2007/05/02 12:48  |
| S8         | 0    | EP-0526171-\$.did.                       | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR                  | ON      | 2007/05/02 12:48  |
| <b>S</b> 9 | 2    | EP-526171-\$.did.                        | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR                  | ON      | 2007/05/02 12:51  |
| S10        | 0    | WO-0126639-\$.did.                       | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR                  | ON      | 2007/05/02 12:49  |
| S11        | 1    | WO-200126639-\$.did.                     | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR                  | ON      | 2007/05/02 13:14  |
| S12        | 1    | ("4816484").PN.                          | US-PGPUB;<br>USPAT                          | OR                  | OFF     | 2007/05/02 12:51  |
| S13        | O    | EP-0196222-\$.did.                       | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR                  | ON      | 2007/05/02 12:51  |

#### **EAST Search History**

| S14 | 1   | EP-196222-\$.did.  | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 12:51 |
|-----|-----|--|---|----|-----|------------------|
| S16 | 987 | (562/444,445) CCLS.  | US-PGPUB;<br>USPAT;<br>USOCR                | OR | OFF | 2007/05/02 13:15 |
| S17 | 585 | S16 and @ad<="20020311"  | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:22 |
| S18 | 29  | nateglinide.clm. and<br>@ad<="20020311"                        | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:32 |
| S19 | 3   | ("6559188").URPN.  | USPAT                                       | OR | ON  | 2007/05/02 13:25 |
| S20 | 0   | ("6878749").URPN.  | USPAT                                       | OR | ON  | 2007/05/02 13:28 |
| S21 | 0   | ("6949555").URPN.  | USPAT                                       | OR | ON  | 2007/05/02 13:29 |
| S22 | 262 | nateglinide.clm. or repaglinide.<br>clm. and @ad<="20020311"   | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:30 |
| S23 | 0   | "nateglinide.clm. or repaglinide.<br>clm." and @ad<="20020311" | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:31 |
| S24 | 0   | "salts of nateglinide.clm." and<br>@ad<="20020311"             | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:31 |
| S25 | 0   | "salts of nateglinide"   | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:31 |
| S26 | 0   | "salt of nateglinide"  | US-PGPUB;<br>USPAT;<br>EPO; JPO;            | OR | ON  | 2007/05/02 14:32 |
|     |     |  | DERWENT                                     |    |     |                  |
| S27 | 46  | salt adj5 nateglinide  | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 13:32 |
| S28 | 5.  | S27 and @ad<="20020311"  | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR | ON  | 2007/05/02 14:33 |
| S29 | 3   | ("2001/0016586").URPN.   | USPAT                                       | OR | ON  | 2007/05/02 13:33 |

#### **EAST Search History**

| S30 | 0    | ("2006/0004102").URPN.       | USPAT                                       | OR   | ON | 2007/05/02 14:12 |
|-----|------|------------------------------|---|------|----|------------------|
| S31 | 0    | ("2007/0043117").URPN.       | USPAT                                       | OR   | ON | 2007/05/02 14:31 |
| S32 | 358  | nateglinide adj5 repaglinide | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 14:33 |
| S33 | 45   | S32 and @ad<="20020311"      | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 14:51 |
| S34 | 0    | WO-03076393-\$.did.          | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 14:51 |
| S35 | 1    | WO-2003076393-\$:did.        | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 14:51 |
| S36 | 1462 | "514/563".CCLS.              | US-PGPUB;<br>USPAT;<br>USOCR                | OR   | ON | 2007/05/02 17:05 |
| S37 | 836  | "562/450".CCLS.              | US-PGPUB;<br>USPAT;<br>USOCR                | OR   | ON | 2007/05/02 17:06 |
| S38 | 617  | "514/62".CCLS.               | US-PGPUB;<br>USPAT;<br>USOCR                | OR   | ON | 2007/05/02 17:07 |
| S39 | 512  | "536/55.3".CCLS.             | US-PGPUB;<br>USPAT;<br>USOCR                | OR   | ON | 2007/05/02 17:08 |
| S40 | 792  | S36 and @ad<="20020311"      | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR . | ON | 2007/05/02 17:08 |
| S41 | 295  | S37 and @ad<="20020311"      | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 17:09 |
| S42 | 359  | S38 and @ad<="20020311"      | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 17:09 |
| S43 | 320  | S39 and @ad<="20020311"      | US-PGPUB;<br>USPAT;<br>EPO; JPO;<br>DERWENT | OR   | ON | 2007/05/02 17:09 |

#### => d his

L7

(FILE 'HOME' ENTERED AT 17:49:04 ON 02 MAY 2007)

FILE 'REGISTRY' ENTERED AT 17:49:18 ON 02 MAY 2007

L1 STRUCTURE UPLOADED

L2 5 S L1 SSS SAM

L3 82 S L1 SSS FULL

FILE 'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007

L4 44 S L3/P

L5 14 S SALT? AND L4

E US20050234129/PRN, PN, AN

E US200500234129/PRN,PN,AN

E NATEGLINIDE+ALL/CT

L6 0 S SALT? (W) NATEGLINIDE

1 S "NATEGLINIDE SALT?"

E US2005234129/PRN, PN, AN

FILE 'STNGUIDE' ENTERED AT 18:00:24 ON 02 MAY 2007

L8 0 S 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524

FILE 'REGISTRY' ENTERED AT 18:04:27 ON 02 MAY 2007

L9 9 S 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524

FILE 'STNGUIDE' ENTERED AT 18:06:38 ON 02 MAY 2007

FILE 'HCAPLUS' ENTERED AT 18:07:36 ON 02 MAY 2007

FILE 'STNGUIDE' ENTERED AT 18:08:42 ON 02 MAY 2007

FILE 'HCAPLUS' ENTERED AT 18:14:39 ON 02 MAY 2007

FILE 'REGISTRY' ENTERED AT 18:14:56 ON 02 MAY 2007 L10 0 S 105816-04-4/PRO

FILE 'CASREACT' ENTERED AT 18:15:57 ON 02 MAY 2007

L11 13 S 105816-04-4/PRO

| SINCE FILE TOTAL                         | 0.90 416.59         | SINCE FILE TOTAL                           |                     |
|--|---------------------|--|---------------------|
| => file casreact<br>COST IN U.S. DOLLARS | FULL ESTIMATED COST | DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | CA SUBSCRIBER PRICE |

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FILE CONTENT: 1840 - 29 Apr 2007 VOL 146 ISS 19

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This file contains CAS Registry Numbers for easy and accurate substance identification

13 105816-04-4/PRO => s 105816-04-4/pro

=> d ll1 ibib abs

L11 ANSWER 1 OF 13 CASREACT COPYRIGHT 2007 ACS on STN ACCESSION NUMBER:

146:163187 CASREACT
Preparation of H type nateglinide crystal
Chen, Songnian; Peng, Qianjian; Yu, Yingmin
Hangzhou Pollen Co., Ltd., Peop. Rep. China
Faming Zhuanli Shenqing Gongkai Shuomingshu, 5pp. PATENT ASSIGNEE (S) : INVENTOR (S): SOURCE:

chi nese Patent DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

APPLICATION NO. DATE KIND DATE PATENT NO.

CN 1887858
CN 1887858
PRIORITY APPLN. INFO.:
AB The title method comprises the steps of: (1) condensing

searched 5/2/07 Page 1

# 10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

trans-4-isopropylcyclohexanecarbonylchloride with D-phenylalanine to obtain crude crystal of B type nateglinide, (2) dissolving the crude crystal in the solution of methanol, aminomethane and water (volume ratio of 60:20:20), heating to 40:60°C, adding 24 active carbon, decoloring for 7-15 min, filtrating, cooling to 10°C to precipitate, filtrating, washing with 40\* ethanol till neutral, and drying to obtain H type nateglinide crystal, and (3) recrystg, the mother solution to obtain H type nateglinide crystal.

#### => d ll1 ibib abs 1-13

PRIORITY APPIN. INFO.:

The title wethod comprises the steps of: (1) condensing the title wethod comprises the steps of: (1) condensing the title wethod comprises the steps of: (1) condensing the crude crystal of B type nateglinide, (2) dissolving the crude crystal in the solution of methanol, annomethane and water (volume ratio of 60.20.20), heating to 40.60°C, adding 2% active carbon, decoloring for 7-15 min, filtrating, cooling to 10°C to precipitate, filtrating, washing with 40% ethanol till neutral, and drying to obtain H type nateglinide crystal, and (2) recrysts, the mother solution to obtain H type nateglinide crystal. The product of H type nateglinide crystal has good L11 ANSWER 1 OF 13 CASREACT COPYRIGHT 2007 ACS on STN
146:163187 CASREACT
TYTLE:
TYTLE:
INVENTOR(S):
Chen, Songnian; Feng, Qianjian; Yu, Yingmin
PATENT ASSIGNEE(S):
Hangzhou Pollen Co., Ltd., Peop. Rep. China
SOURCE:
CODEN: CANXEV CN 2006-10052617 20060721 CN 2006-10052617 20060721 APPLICATION NO. 20070103 Patent Chinese KIND DATE Ø FAMILY ACC. NUM. COUNT: PATENT INFORMATION: CN 1887858 PATENT NO. DOCUMENT TYPE:

L11 ANSWER 2 OF 13 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 145:103952 CASREACT
TITLE: Process for the preparation of nateglinide, preferably in B-form Vigano, Enrico; Pizzatti, Enrica; Lanfranconi, Simona; Molteni, Renato; Landonio, Ernesto Italy U.S. Pat. Appl. Publ., 22 pp. CODEN: USXXCO English PATENT ASSIGNEE (S) : DOCUMENT TYPE: INVENTOR (S): LANGUAGE:

APPLICATION NO. DATE KIND DATE PATENT NO.

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

isopropylcyclohexancarboxylicacid in the presence of an acyl chloride or earbonylalimidazole, optionally isolating the nateglinide Me ester obtained and re-dissolving it in a second organic solvent, (i)) addition of water and alkali hydroxide to the reaction mixture and separation of the PRIORITY APPLA. INFO.:

US 2005-28283 20050103

AB The invention relates to a process for the preparation of nateglinide, preferably in B-form, substantially free from the H-form, comprising three steps starting from (i) reaction in an organic solvent between D-phenylalanine Me ester or a salt and trans-4-US 2005-28283 US 2005-28283 20060706 A1 adneons

phase containing the alkali salt of nateglinide, and (iii) addition of hydrochloric acid to the aqueous phase from step (ii) to obtain nateglinide. In an example, the reaction was carried out in acetone in the presence of triethylamine and Et chloroformate and hydrolysis of nateglinide Me ester was carried out using tolune, tricaprylmethylammoniumchloride, and aqueous potassium hydroxide to afford nateglinide in B-form (130.44°C).

144:51894 CASREACT
One-pot process for the preparation of nateglinide
Cankan, Rajendra Narayanrao; Rao, Dharmaraj
Ramachandra, Singh, Manjinder; Birari, Dilip Ramdas
Cipla Limited, India; Wain, Christopher Paul
CODEN: 1XXD2. CASREACT COPYRIGHT 2007 ACS on STN Patent English COUNT: L11 ANSWER 3 OF 13 ACCESSION NUMBER: PATENT ASSIGNEE (S): LANGUAGE: FAMILY ACC. NUM. CC PATENT INFORMATION DOCUMENT TYPE: INVENTOR(S): SOURCE:

APPLICATION NO. DATE KIND PATENT NO.

# 8 X X X X A Y Y A DK, EE, ES, FI, FR, GB, GR, HU, PL, PT, RO, SE, SI, SK, TR GB 2004-13084 20040611 WO 2005-GB2267 20050608 SG, KR, EL, 20050608 20050608 ₩₩. ₩₩. ₩₩. ¥3.48 20050608 MC, CK, BW, KG, KG, SC, US, AU 2005-252002 CA 2005-2570041 EP 2005-750279 2005-GB2267 SZ, BG, LT, CM, B, B, B, SL, BE, IT, CI, BG, FC, WA, WA, SD, AT, IS, OG, IS, PT, ş CF, TE, 田片 TH. LEK. 20070328 CY, CZ, LU, MC, MW, RU, GR, 20051222 A R C C B R 20051222 20051222 AT, CZ, HU, LT, TM, LS, AB, TG, TG, R: AT, BE, BG, CH, IS, IT, LI, LT, IS, IT, PRIORITY APPLN. INFO. AU 2005252002 CA 2570041 EP 1765769 WO 2005121071 GE, LC, NG, SL, ZA, BW, RW:

A one-pot process for the preparation of nateglinide is presented which comprises amidation of a C1-4 alkyl ester of D-phenylalanine, either as the free base or in salt form (typically the hydrochloride), with MARPAT 144:51894 OTHER SOURCE(S): B

searched 5/2/07 Page 3

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

trans-4-isopropylcyclohexanecarboxyliacid or its acid halides to obtain a C1-4 alkyl ester of nateglinide, preferably the Me ester of nateglinide, followed by alkali (e.g., NaOH) saponification and acidification (e.g., HCI) to yield nateglinide (m.p. 128-131°).

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

COPYRIGHT 2007 ACS on STN CASREACT L11 ANSWER 4 OF 13 ACCESSION NUMBER:

Improved process for the preparation of hypoglycemic agent nateglinide
Zhong, Bohua; Mu, Bo; Yan, Yuan
Toxic Drug Inst., Academy of Military Medical Science, PLA, Peop. Rep. China
Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. 143:97635 CASREACT INVENTOR(S): PATENT ASSIGNEE(S):

SOURCE:

given CODEN: CNXXEV Patent

Chinese COUNT: FAMILY ACC. NUM. CO PATENT INFORMATION:

DOCUMENT TYPE:

A scalable process for the preparation of nateglinide, a hypoglycemic agent, was reported. The key improvement is that the acylation of D-phenylalanine with 4-isopropylcyclohexanecarbonylchloride was performed under a homogeneous condition using a mixture of dioxane or THF and H2O as solvent, largely increasing the yield. Other features include the use of cheap Pd/C instead of previously expensive PtO2 as hydrogenation catalyst in the reduction of 4-isopropylbenzoicacid into 4-isopropylcyclohexanecarboxylicacid. Purification of nateglinide by r in petroleum ether, hexane and cyclohexane or their mixts. is claimed. 20030117 20030117 CN 2003-100559 CN 2003-100559 APPLICATION NO. 20040804 DATE KIND Æ PRIORITY APPLN. INFO.: CN 1517335 PATENT NO.

recrystn

L11 ANSWER 5 OF 13 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:26875 CASREACT
TITLE: Improved process for the preparation of hypoglycemic Zhu, Qin; Pan, Junfang; Shi, Mingfeng Shanghai Hushuo Medicina Science & Technology Vevelopment Co., Ltd., Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. agent nateglinide PATENT ASSIGNEE (S) INVENTOR (S)

CODEN: CNXXEV Patent Chinese given DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION

PRIORITY APPLN. INFO.: AB A scalable process for the preparation of nateglinide, a hypoglycemic agent, 20030117 CN 2003-114970 CN 2003-114970 20040804 KIND DATE ď CN 1517334 PATENT NO.

was reported. The key improvement is that the acylation of under with 4-isopropylcyclohexanecarbonylchloride was performed under a homogeneous condition using a mixture of DME and H2O as solvent, largely increasing the yield. Other features include the use of cheap Pd/C instead of previously expensive PtO2 as hydrogenation catalyst in the reduction of 4-isopropylbenzoicacid into 4-isopropylcyclohexanecarboxylic acid.

| L11 ANSWER 6 OF 13 CASREACT COPYRIGHT 2007 ACS on STN | 143:7982 CASREACT | Process for the preparation of the crystalline B-form | nateglinide from D-phenylalanine methyl ester and | trans-4-isopropylcyclohexanecarboxylicacid | Vigano', Enrico; Pizzati, Enrica; Lanfranconi, Simona; | Molteni, Renato; Landonio, Ernesto | A.M.S.A. Anonima Materie Sintetiche e Affini S.p.A., | Italy | Eur. Pat. Appl., 32 pp. | CODEN: EPXXDW | Patent         | English   |                         |                     |  |
|---|-------------------|---|---|--|--|------------------------------------|--|-------|-------------------------|---------------|----------------|-----------|-------------------------|---------------------|--|
| L11 ANSWER 6 OF 13 CAS                                | ACCESSION NUMBER: | TITLE:  |   |  | INVENTOR(S):   |                                    | PATENT ASSIGNEE (S):                                 |       | SOURCE:                 |               | DOCUMENT TYPE: | LANGUAGE: | FAMILY ACC. NUM. COUNT: | PATENT INFORMATION: |  |

PRIORITY APPIN. INFO:

BP 2003-27114 20031126

AB A process for the preparation of nateglinide comprises: (I) the amidation reaction in a first organic solvent between D-phenylalanine Me ester, or a salt, and trans-4-isopropylcyclohexanecarboxylicacid and an acyl chloride, or carbonyldinidazole, to obtain the nateglinide Me ester; (Ia) optionally isolating the nateglinide Me ester and redissolving it in a second organic solvent to give a solution; (II) addition of water and alkali hydroxide to the reaction mixture coming from step (I) without isolating the nateglinide Me ester, or, if applicable, to the solution of step (Ia), and separation of the aqueous phase containing the alkali salt of nateglinide; Į, EP 1535900 A1 20050501 — EP 1535900 B1 20051227 EP 1535900 B1 20051227 EP 1535900 B1 20051227 EP 1535900 B1 20051227 EP 1535900 EP 1535900 EP 15. UV, EI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK AT 349418 T 20070115 EP 2003-27114 20031126 EP 2003-27114 20031126 APPLICATION NO. DATE DATE KIND PATENT NO.

of hydrochloric acid to the aqueous phase coming from step (II) to obtain nateglinide, wherein the organic solvent employed in step (II) is a water non-miscible solvent. REFERENCE COUNT: (III) addition

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
L11 ANSWER 7 OF 13 CASREACT COPVRIGHT 2007 ACS on STN
ACCESSION NUMBER:
TITLE:
An efficient large scale synthesis of nateglinide
AUTHOR(S):
Charles and Author (S):
Sameer J.; Gaikwad, Nandakumar B.; Kulkarni, Pramila
V.; Bhirud, Shekar B.
CORPORATE SOURCE:
Process Research and Development, Glenmark Research
Centre, MIDC Mahape, Navi Mumbai, 400709, India
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searched 5/2/07 Page 5

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

| as prep<br>ropylcy<br>th D-phe   |   | Patent<br>English<br>ION:   | PATENT NO. KIND DATE APPLICATION NO. DATE  WO 2005005373 A1, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CA, CR, CR, CR, CR, CR, CR, CR, CR, CR, CR  |
|--|---|---|--|
| SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: AB Nateglinide wa. rans-4-isopro Carbonate with REFERENCE COUNT: LII ANSWER 8 OF 13 ACCESSION NUMBER: TITLE: | INVENTOR(S): PATENT ASSIGNEE(S) SOURCE: | DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COI PATENT INFORMATION: | MO 2005005373 WO 2005005373 WO 2005005373 WO CO, C G GH, G G G GH, G G G G G G G GH, G |

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AB W. ((trans-4-isopropylcyclohexyl)-D-phenylalanin(nateglinide) was prepared by reaction of trans-4-isopropylcyclohexyl)-D-phenyllcyclohexylcarboxyliacid with an alkyl chloroformatein a ketonic solvent in the presence of a base at 20 to 30°C and reaction of the mixed anhydride product with an aqueous alkali salt solution of D-phenylalanine. An example shows the synthesis of nateglinide by using triethylamine and Et chloroformatein acetone (97% pure following HPLC).

THERE ARE I CITED REFERENCES AVAILABLE FOR THIS
       140:199745 CASREACT
Synthesis and purification of nateglinide
Naik, Samir Jaivant, Rulkarni, Pramila Vijay, Gaikwad,
Naik, Samir Jaivant, Rulkarni, Pramila Vijay, Gaikwad,
Nandkumar Baburao, Sawant, Mangesh Shivram, Bhirud,
Shekhar, Batchu, Chandrasekhar
Pollamark Pharmaceuticals Limited, India
Por Int. Appl., 28 pp.
Patent
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Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
PCT Int. Appl., 31 pp.
CODEN: PIXXDZ
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PRIORITY APPLN. INFO.:
                                                                                                                                                                                                                   AE, AG, CR, CO, CR, CO, CR, LI, LS, LT, TR, TT, CH, CM, CG, KZ, KZ, FI, FR, BF, BJ,
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        L11 ANSWER 10 OF 13
ACCESSION NUMBER:
 13
                                                                       PATENT ASSIGNEE(S):
                                                                                                                                                                                                                                                                                                                                            IN 2002MU00773
                                                                                                                                                                                            WO 2004018408
WO 2004018408
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 PATENT ASSIGNEE(S)
L11 ANSWER 9 OF ACCESSION NUMBER:
                                                                                                                                                                                                                                                                                                                                                                                          OTHER SOURCE(S):
AB N-[(trans-4
                                                                                                                                                                     PATENT NO.
                                                                                                           DOCUMENT TYPE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               DOCUMENT TYPE:
LANGUAGE:
                                   INVENTOR (S):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         INVENTOR (S):
                                                                                                                                                                                                                                                                                              RW:
                                                                                                                        LANGUAGE
                                                                                   SOURCE:
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 TITLE:
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Page 7 searched 5/2/07

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

AB A process for the preparation of nateglinide involves converting trans-4-isopropy/cyclohexanecarboxy/lacid into the acid chloride by reaction with thionyl chloride in the presence of an organic amide and acylation of a suitable salt of D-phenylalanine with the acid chloride in a sylation of a suitable salt of D-phenylalanine with the acid chloride in a single or two phase system or in water free of a co-solvent.

REFERENCE COUNT:

6 RECORD. ALL CITATIONS AVAILABLE FOR THIS REFERENCE SAVAILABLE FOR THIS A R R R R PT, ES, TR, A KK GG SK, AZ, SK, 20021105 SE, HU, 485.85 485.85 AM, DK, SI, 20030718 20030718 20021212 20030123 20030224 20030616 20030703 20030718 20020925 20020926 20609002 GB, GR, IT, LI, LU, NL, CY, AL, TR, BG, CZ, EE, US 2003-623290 2 US 2003-622999 2 US 2003-622999 2 US 2005-516363 2 US 2005-3949495 2 US 2002-413629 2 US 2002-413629 2 US 2002-413629 2 US 2003-449791P 2 US 2003-449791P 2 US 2003-47991P 2 US 2003-622999 2 US 2003-622999 FI, KR, KZ, ZM, ZM, KO, MR, WO 2003-US21238 APPLICATION NO. AU 2003-256454 EP 2003-763310 CN 2003-817439 US 2003-623237 MK, MN, SD, SE, VC, VN, SL, SZ, BB, BG, GN, GO, AZ, DM, IIS, SC, SC, SD, AT, IIT, GA, Ж. Ж. 20040123 DK, ES, FI, RO, 20040617 20061212 20050120 20050407 20060118 20070104 20040115 20050921 # 2 B B 2 B 띰, 8 KIND A1 E 5 PRIORITY APPLN. INFO.: SI, BE, 2004116526 WO 2004005240 2003256454 2005014949 2005075400 RG TR CR CN 1671649 US 20041165 US 7148376 US 20050149 US 20050754 CN 1723190 US 20070048 PATENT NO. RW: ж :: AO EP

Page 8 searched 5/2/07

CASREACT COPYRIGHT 2007 ACS on STN 138:254901 CASREACT a new synthesis method of nateglinide as antidiabetic

L11 ANSWER 11 OF 13 ACCESSION NUMBER:

TITLE:

AUTHOR(S): CORPORATE SOURCE:

drug , Mang, Yiheng; Gong, Ping; Zhao, Yanfang School of Pharmaceutical Engineering, Shenyang Temperaceutical University, Shenyang, 110016, Peop. Rep. China

Zhongguo Yaowu Huaxue Zazhi (2002), 12(2), 94-96 CODEN: ZYHZEF; ISSN: 1005-0108

PUBLI SHER:

A new antidiabetic drug-nateglinide was synthesized from isopropylbenzene by Friedel-Crafts reaction, chloroform reaction, catalytic hydrogenation to obtain trans-4-isopropylhevanecarboxylicacid, acylation of D-phenylalanine Et ester, hydrolysis to obtain nateglinide B-type crystal, and crystal-conversion. The total yield was 9.8% Zhongguo Yaowu Huaxue Zazhi Bíanjibu Journal CASREACT COPYRIGHT 2007 ACS on STN Chinese 13 L11 ANSWER 12 OF ACCESSION NUMBER: DOCUMENT TYPE: LANGUAGE: AB A new antic

136:340997 CASREACT
Process for preparation of acylphenylalanines
Sumikawa, Michito; Ohgane, Takao
Ajinomoto Co., Inc., Japan
PCT Int., Appl., 14 pp.
CODEN: PIXXD2
Patent Japanese LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: INVENTOR(S): PATENT ASSIGNEE(S) SOURCE: DOCUMENT TYPE:

EP 2001-974874 20011016
EP, GB, GR, IT, LL, LU, NL, SE, MC, PT, MK, CY, AL, TR
BR 200114728 20011016
RU 2003-111012 20011017
IN 2003-611012 20011017
IN 2003-418102 20030411 8.8.4.9.8 CY, BF, # H H H H 급, 다 LC. 99 BE, 20051228 AT, UG, ZW, I MC, NL, I MR, NE, I MZ, AZ, APPLICATION NO. S X X SZ, TZ, UIT, LU, N BG, KG, TJ, Ş DE, DK, ES, FR, G LV, FI, RO, MK, C 20031014 22 20061120 3 20040211 AZ, DM, IS, MG, SI, 888 20030410 20050415 20040205 20060418 20060713 DATE AL, AM, AT, CC, CE, DE, HU, ID, ILL, IV, MA, RU, SD, SE, WN, YU, ZA, RE, FF, FR, CG, CI, CM, CG, CI, CM, KIND 8 P P B C P R: AT, BE, CH, PRIORITY APPLN. INFO.: BR 2001014728 RU 2287520 TW 575541 IN 2003CN00536 US 2004024219 US 7030268 US 2006155143 WO 2002032853 200194264 AU 20019426 CA 2425533 EP 1334962 PATENT NO. RM: 3

This document discloses a process for preparing easily and simply high-purity acylphenylalanines extremely useful as raw materials of drugs or the like, characterized by reacting an acid chloride with phenylalanine in a mixed solvent consisting of an organic solvent and water under conditions made 20001018 20011016 20030418 US 2005-319177 JP 2000-317603 WO 2001-JP9068 US 2003-418102 AB

with potassium hydroxide. REFERENCE COUNT: alkaline

searched 5/2/07

Page 9

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

-str\_regno\_text -Search NATEGLINIDE

116:325825 CASRRACT
Process for producing nateglinide crystals
Takahashi, Dalsuke; Nishi, Selichi; Takahashi, Satoji
Alinomoto Co., Inc., Japan
PCT Int. Appl., 14 pp.
Patent 58478 GY, BF, AU 2001-94265 20011016
CA 2001-2425538 20011016
EP 2001-974875 20011016
EP 2001-974875 20011016
K, CY, AL, TR
ER 2001-14729 20011016
CAV 2005-111021 20011016
TW 2001-90125697 20011017
IN 2001-90125697 20030411
US 2003-418105 20030418 8 H K B B 를 다. 5. 5. SE, , ZW, AT, BY, NL, PT, SN, NE, SN, DATE BZ, GB, KZ, NO, BR, BY, ES, FI, KP, KR, MX, MZ, I APPLICATION NO. CASREACT COPYRIGHT 2007 ACS on STN Æ SL, SZ, TZ, U IE, IT, LU, N GQ, GW, ML, N BB, BG, I EC, EE, I KE, KG, I MN, MW, I SL, TJ, AZ, DM, IS, MG, SI, 888 R: AT, BE, CH, DE, DK, ES, FR, IE, SI, LT, LV, FI, RO, MK, 2001014729 A 20031014 20020429 20030410 20030813 AU, DK, IN, IN, XMD, GB, GB, WO 2002032854 A1 200204;
W: AE, AG, AL, AH, AT, AI,
CO, CR, CU, CZ, DE, DE,
CM, HR, HU, ID, IL, IN,
LS, LT, LU, LV, MA, MI
PT, RO, RU, SD, SE, SC,
WS, UZ, WN, YU, ZA, ZY,
RM: GH, AH, AH, RE, LS, MW, MA
DE, DK, ES, FI, FR, GE
DE, DK, ES, FI, FR, GE
DE, DK, CG, CI, CW, GF, Japanese KIND DATE LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: 13 PATENT ASSIGNEE (S): AU 200194265 CA 2425538 EP 1334963 L11 ANSWER 13 OF ACCESSION NUMBER: PATENT NO. DOCUMENT TYPE: TITLE: INVENTOR(S): SOURCE:

H 20001018 20060410 20060510 20060321 20050415 20040212 20070424 BR 2001014729 RU 2273629 CN 1769263 TW 251588 IN 2003CN0637 US 2004030182 US 7208622 PRIORITY APPLN. INFO.

A process for producing nateglinide crystals comprises reacting trans-4-isopropy/cyclohexylcarbonylchloride with D-phenylalanine in a mixed solvent consisting of a ketone solvent and water in the presence of an alkali to obtain a reaction mixture containing nateglinide, adding an acid 20011016 JP 2000-317604 CN 2001-820658 WO 2001-JP9069 AB

the reaction mixture to make it acidic, and regulating (a) the temperature to 58° to 72° and (b) and the ketone solvent concentration to > 8 weight\* and < 22 weight\*, to conduct crystallization Nateglinide is a known 2

The process is an industrially advantageous method for crystallizing nateglinide. antidiabetic.

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT REFERENCE COUNT:

d his ٨ (FILE 'HOME' ENTERED AT 17:49:04 ON 02 MAY 2007)

FILE 'REGISTRY' ENTERED AT 17:49:18 ON 02 MAY 2007

E. STRUCTURE UPLOADED

S IL SSS SAW

13 82 S. L. SSS FULL

FILE 'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007

L4 4 S. L3/P

L5 14 S. SALT? AND L4

E USZO050234129/PRN, PN, AN

E USZO050234129/PRN, PN, AN

E USZO050234129/PRN, PN, AN

E NATECLINIDE.ALL/CT

L6 0 S. SALT?

E USZO050234129/PRN, PN, AN

E USZO050234129/PRN, PN, AN

E USZO050234129/PRN, PN, AN

E USZO050234129/PRN, PN, AN

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E USZO05234129/PRN, PN, AN

FILE 'STNGUIDE' ENTERED AT 18:00:24 CN 02 MAY 2007 L8 0 S 105816-04-4/RNOR 592523-31-4/RNOR 592523-32-5/RNOR 592524

FILE 'REGISTRY' ENTERED AT 18:04:27 ON 02 MAY 2007 L9 9 S 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524

FILE 'STNGUIDE' ENTERED AT 18:06:38 ON 02 MAY 2007

FILE 'HCAPLUS' ENTERED AT 18:07:36 ON 02 MAY 2007

FILE 'STNGUIDE' ENTERED AT 18:08:42 ON 02 MAY 2007

FILE 'HCAPLUS' ENTERED AT 18:14:39 ON 02 MAY 2007

FILE 'REGISTRY' ENTERED AT 18:14:56 ON 02 MAY 2007 L10 0 S 105816-04-4/PRO FILE 'CASREACT' ENTERED AT 18:15:57 ON 02 MAY 2007 L11 13 S 105816-04-4/PRO

chain nodes:

1 2 3 4 5 18 19 20 21 22 23

ring nodes:

6 7 8 9 10 11 12 13 14 15 16 17

chain bonds:

1-2 1-10 1-18 2-3 3-4 3-20 4-5 4-19 7-21 13-20 21-22 21-23

ring bonds:

6-7 6-11 7-8 8-9 9-10 10-11 12-13 12-17 13-14 14-15 15-16 16-17

exact/norm bonds:

1-2 1-18 2-3 6-7 6-11 7-8 8-9 9-10 10-11

exact bonds:

1-10 3-4 3-20 7-21 13-20 21-22 21-23

normalized bonds:

4-5 4-19 12-13 12-17 13-14 14-15 15-16 16-17

#### Match level:

1:CLASS2:CLASS3:CLASS4:CLASS5:CLASS6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS19:CLASS20:CLASS21:CLASS22:CLASS 23:CLASS

#### Stereo Bonds:

10-1 (Single Wedge).

21-7 (Single Hash).

#### Stereo Chiral Centers:

7 (Parity=Even) 10 (Parity=Odd)

#### Stereo RSS Sets:

Type=Relative (Default). 2 Nodes= 7 10

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10/507255 SALTS OF NATEGLINIDE -str_regno_text -Search
=> d his
     (FILE 'HOME' ENTERED AT 17:49:04 ON 02 MAY 2007)
     FILE 'REGISTRY' ENTERED AT 17:49:18 ON 02 MAY 2007
L1
                STRUCTURE UPLOADED
L2
              5 S L1 SSS SAM
L3
             82 S L1 SSS FULL
     FILE 'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007
L4
             44 S L3/P
L5
             14 S SALT? AND L4
                E US20050234129/PRN, PN, AN
                E US200500234129/PRN, PN, AN
                E NATEGLINIDE+ALL/CT
L6
              0 S SALT? (W) NATEGLINIDE
L7
              1 S "NATEGLINIDE SALT?"
                E US2005234129/PRN, PN, AN
     FILE 'STNGUIDE' ENTERED AT 18:00:24 ON 02 MAY 2007
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L8 0 S 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524 FILE 'REGISTRY' ENTERED AT 18:04:27 ON 02 MAY 2007 9 S 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524 L9

searched 5/2/07

=> Uploading C:\Program Files\Stnexp\Queries\2007 cases\10507255\nateglinide.str H

STRUCTURE UPLOADED

=> d 11 L1 HAS NO ANSWERS L1 STR

Structure attributes must be viewed using STN Express query preparation.

=> s 11 sss sam SAMPLE SEARCH INITIATED 17:50:02 FILE 'REGISTRY' SAMPLE SCREEN SEARCH COMPLETED - 441 TO ITERATE

441 ITERATIONS 100.0% PROCESSED SEARCH TIME: 00.00.01

5 ANSWERS

10079 ONLINE \*\*COMPLETE\*\*
BATCH \*\*COMPLETE\*\*
7561 TO 10075
5 TO 234 FULL FILE PROJECTIONS: PROJECTED ITERATIONS: PROJECTED ANSWERS:

5 SEA SSS SAM L1 17 => s 11 sss full FULL SEARCH INITIATED 17:50:10 FILE 'REGISTRY' FULL SCREEN SEARCH COMPLETED - 9018 TO ITERATE

9018 ITERATIONS 100.0% PROCESSED SEARCH TIME: 00.00.01

82 SEA SSS FUL L1 ដ

searched 5/2/07 Page 1

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

TOTAL SESSION 172.76 ENTRY 172.55 SINCE FILE => fil hcaplus COST IN U.S. DOLLARS FULL ESTIMATED COST

FILE 'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STR CUSTOWER AGREEMENT.
PLEASE SEE "HELP USAGETERNS" FOR DETAILS.
POPPRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

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VOL 146 ISS 19 (20070501/ED) FILE COVERS 1907 - 2 May 2007 FILE LAST UPDATED: 1 May 2007 New CAS Information Use Policies, enter HELP USAGETERMS for details.

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44 L3/P => s 13/p L4

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=> d scan

HCAPLUS COPYRIGHT 2007 ACS on STN 14 ANSWERS ICM C07C231 ដូដ

C07C233-63; A61K031-16; A61P003-00

63-6 (Pharmaceuticals) ပ္ပ

Section cross-reference(s): 34, 75
Process for the preparation of polymorphic crystalline forms of mateglinide ammonium salt nateglinide ammonium salt belymorphic cryst form Bicarbonates I

ST

RL: RGT (Reagent): RACT (Reactant or reagent)
(Group IA and IIA metal, bases; process for the preparation of polymorphic
crystalline forms of nateglinide ammonium salt) Carbonates, reactions

Alkali metal hydroxides

H

(base; process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt)
Alkali metal hydrides
Alkaline earth hydroxides
RL: RGT (Reagent); RACT (Reactant or reagent) RL: RGT (Reagent); RACT (Reactant or reagent)

Ħ

82 ANSWERS

ğ (bases; process for the preparation of polymorphic crystalline forms nateglinide ammonium salt)

Crystallization Neutralization H

(in a process for the preparation of polymorphic crystalline forms

ğ

ammonium salt) Ħ

nateglinide

Bases, reactions
RI: RGT (Reagrant), RACT (Reactant or reagent)
(in a process for the preparation of polymorphic crystalline forms of

nateglinide

ammonium salt)

H

Diabetes mellitus (non-insulin-dependent; process for the preparation of polymorphic crystalline

forms of nateglinide ammonium salt for the treatment of) H

Polymorphism (crystal) (process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt)

Hyperglycemia II

(process for the preparation of polymorphic crystalline forms of nateglinide authorium salt for the treatment of)

II

II

Antidiabetic agents
(process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt for use as)

Drug delivery systems
(process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt for use in)

134-28-1D. Alumina, basic

RI. RGT (Reagent): RACT (Reactant or reagent)
(base; process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt)

II

II

67-56-1, Methanol, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt) Ħ

594837-89-5P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt)

1336-21-6, Ammonium hydroxide 7664-41-7, Ammonia, reactions 105816-04-4, Nateglinide RL: RCT (Reactant); RACT (Reactant or reagent) (process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt)

H

MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):3 HOM HCAPLUS COPYRIGHT 2007 ACS on 14 ANSWERS ICM C07C231-ICS C07C233-

STN

C07C231-14

34-2 (Amino Acids, Peptides, and Proteins)
Synthesis and purification of nateglinide
nateglinide prepn purifn; phenylalanine isopropylcyclohexylcarbonyl prepn
purifn 105816-04-4P, Nateglinide
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN
(Synthetic preparation); PREP (Preparation) 

searched 5/2/07

Page 3

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

79-22-1, Methyl chloroformate 108-23-6, Isopropyl chloroformate 109-61-5, Propyl chloroformate 541-41-3, Ethyl chloroformate 673 D Phenylalanine 7077-05-6, trans 4 Isopropylcyclohexanecarboxylic RI. RCT (Reactant); RACT (Reactant or reagent) (synthesis and purification of nateglinide) synthesis and purification of nateglinide) H

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C07C103-84 C07D307-84; C07C103-737; A61K031-195; A61K031-215 ខ

(Amino Acids, Peptides, and Proteins) on cross-reference(s): 1

Preparation of D-phenylalanine derivatives and their use as hypoglycemic II

hypoglycemic D phenylalanine prepn Antidiabetics and Hypoglycemics (N-acyl-D-phenylalanines) 6066-82-6, N-Hydroxysuccinimide ST II

RL: RCT (Reactant); RACT (Reactant or reagent)
 (esterification of, with cyclopentanecarboxylic acid and cumic acid) 536-66-3 II

RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification of, with hydroxysuccinimide)
23635-14-5, (S)-(-)-Perillic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrogenation of) H

Ħ

10512-92-2 37002-52-1 74204-45-8 85856-40-2 86808-12-0 study. Since 10512-92-2 and activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study) thypoglycemic activity of) (hypoglycemic activity of) 707-05-6p, trans-4-Isopropylcyclohexanecarboxylic acid 7084-93-7p, cis-4-Isopropylcyclohexanecarboxylic acid RL: RCI (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

H

(Reactant or reagent)

(preparation and esterification of) 371-58-0P 105746-51-8P : RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) 51871-58-0P H

(preparation and reaction of, with D-phenylalanine Me ester) 13828-35-8P, Methyl cis-4-isopropylcyclohexanecarboxylate 13828-36-9P, Methyl trans-4-isopropylcyclohexanecarboxylate 105746-50-7P Ħ

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and saponification of)
62067-45-2P, 4-Isopropylcyclohexanecarboxylic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT H

105746-27-8P 105746-32-5P 105746-37-0P 105746-42-7P 105746-42-7P 105746-26-7P 105746-31-4P 105746-36-9P 105746-41-6P 105746-46-1P (preparation and N-acylation by, of D-phenylalanine)
)1-91-7P 105746-24-5P 105746-25-6P 105746-26-7 105746-49-4P 105816-04-4P 105816-05-5P 105746-29-0P 105746-30-3P 105746-34-7P 105746-35-8P 105746-40-5P 105746-45-0P 105746-39-2P 105746-44-9P 105746-43-8P 105746-48-3P 105746-28-9P .05746-38-1P 75691-91 II

preparation); PREP (Preparation) (preparation of, as hypoglycemic) 13033-84-6 RL: SPN (Synthetic

H

RL: RCT (Reactant); RACT (Reactant or reagent) (reaction of, with carboxylic acid succinimidyl esters) 65-85-0, reactions 98-73-7, 4-tert-Butylbenzoic acid 98-89-5 496-41-3 824-62-4 98-32-9-3 4771-80-6, 3-cyclohexenecarboxylic acid 683-47-2, trans-4-Ethylcyclohexanecarboxylic acid 1531-45-6, 4-Ethylbenzoyl trans-4-Methylcyclohexanecarboxylic acid 1631-45-6, 4-Ethylbenzoyl chloride 38289-27-9 38289-28-0 65898-38-6, 5-Indanecarboxylic acid RI: RCT (Reactant); RACT (Reactant or reagent) ဌ

(N-acylation by, of D-phenylalanine)

673-06-3

H

RI: RCT (Reactant); RACT (Reactant or reagent) (N-acylation of) HCAPLUS COPYRIGHT 2007 ACS on STN

C07C231-24; C07C233-63 ပ္ပ IJ

34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 45, 63, 75
Process for the preparation of the crystalline B-form nategiinide from D-phenylalanine methyl ester and trans-4-isopropylcyclohexanecarboxylic

ST

nateglinide prepn polymorphic crystal B form Acid halides RL: RGT (Reagent); RACT (Reactant or reagent) (acid chlorides; in a process for the preparation of the crystalline B-form nateglinide from D-phenylalanine Me ester)

Amidation Neutralization Ħ

Saponification

(in a process for the preparation of the crystalline B-form nateglinide from D-phenylalanine Me ester)
Alkali metal hydroxides
RL: RGT (Reagent), RACT (Reactant or reagent)
D-phenylalanine Me ester)
Polymorphism (Crystal) II

H

(process for the preparation of the crystalline B-form nateglinide from D-phenylalanine Me ester)

Saponification catalysts (quaternary ammonium compds.; in a process for the preparation of the II

II

B-form nateglinide from D-phenylalanine Me ester) crystalline

Quaternary ammonium compounds, uses
RL: CAT (Catalyst use); USES (Uses)
(saponification catalysts; in a process for the preparation of

nateglinide from D-phenylalanine Me ester) crystalline B-form

the

5137-55-3, Tricaprylmethylammonium chloride RL: CAT (Catalyst use); USES (Uses) (in a process for the preparation of the crystalline B-form nateglinide from H

673-06-3, D-Phenylalanine 7077-05-6, trans-4Isopropylcyclohexanecarboxylic acid 21685-51-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for the preparation of the crystalline B-form nateglinide from D-phenylalanine Me ester) phenylalanine Me ester) II

II

13033-84-6p 105746-47-2P RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

searched 5/2/07 Page 5

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

RI: RGT (Reagent); RACT (Reactant or reagent)
(in a process for the preparation of the crystalline B-form nateglinide from D-phenylalanine Me ester)
105816-04-4P, Nateglinide
RI: PRP (Properties); SPM (Synthetic preparation); PREP (Preparation)
(process for the preparation of the crystalline B-form nateglinide from (in a process for the preparation of the crystalline B-form nateglinide from (process to ture ferer)
D-phenylalanine Me ester)
67-64-1, Acetone, uses 68-12-2, DMF, uses 71-43-2, Benzene, uses 75-69-2, Diciolaromethane, uses 108-98-3, Tolunere, uses 108-90-7, Chlorobenzene, uses 109-9-9, Thf, uses 110-54-3, Hexane, uses 110-71-4, Glyme 110-82-7, Cyclohexane, uses 111-96-6, Diglyme 123-91-1, Dioxane, uses 127-19-5, Dimethylacetamide 142-82-5, Heptane, uses 1732-66-4, NMP, uses 1330-20-7, Xylene, uses 7732-18-5, Water, 1310-58-3, Potassium hydroxide, 1310-73-2, Sodium hydroxide, 7647-01-0, Hydrogen chloride, uses RL: NUU (Other use, unclassified); USES (Uses) D-phenylalanine Me ester) 530-62-1 541-41-3, Ethyl chloroformate reactions 1310-65-2, Lithium hydroxide reactions 3282-30-2, Pivaloyl chloride II H II

(solvent; in a process for the preparation of the crystalline B-form

from D-phenylalanine Me ester) nateglinide

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

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'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007 FILE

44 S L3/P 14 S SALT? AND L4

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ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN 2006:657506 HCAPLUS 145:103952 ACCESSION NUMBER: DOCUMENT NUMBER:

Process for the preparation of nateglinide, preferably in B-form Vigano, Enrico; Pizzatti, Enrica; Lanfranconi, Simona; Molteni, Renato; Landonio, Ernesto INVENTOR(S):

Italy U.S. Pat. Appl. Publ., 22 pp. CODEN: USXXCO PATENT ASSIGNEE (S): SOURCE:

English DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

APPLICATION NO. DATE KIND PATENT NO.

|            | CAPPIN. INFO.: US 2005–28283 20050103 | OURCE(S): CASREACT 145:103952 | The invention relates to a process for the preparation of nateglinide, | oreferably in B-form, substantially free from the H-form, comprising three | steps starting from (1) reaction in an organic solvent between | D-phenylalanine Me ester or a salt and trans-4- | isopropylcyclohexancarboxylic acid in the presence of an acyl chloride or | carbonyldiimidazole, optionally isolating the nateglinide Me ester | obtained and re-dissolving it in a second organic solvent, (ii) addition of | water and alkali hydroxide to the reaction mixture and separation of the |
|------------|---------------------------------------|-------------------------------|--|--|--|---|---|--|---|--|
| US 2006148 | PRIORITY APPLN. INFO.:                | OTHER SOURCE(S):              | AB The invent:   | preferably   | steps star   | D-phenylal                                      | isopropylc  | carbonyldi   | obtained a  | water and  |

ester nd aqueous phase containing the alkali salt of nateglinide, and (iii) addition of hydrochloric acid to the aqueous phase from step (ii) to obtain nateglinide. In an example, the reaction was carried out in acetone in the presence of

|     | triethylamine and E     | triethylamine and Et chloroformate and hydrolysis of nateglinide Me este |
|-----|-------------------------|--|
|     | was carried out usi     | was carried out using toluene, tricaprylmethylammonium chloride, and agu |
|     | potassium hydroxide     | potassium hydroxide to afford nateglinide in B-form (130.44°C).          |
| 1   | 5 ANSWER 2 OF 14 HCA    | L5 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN                      |
| æ   | ACCESSION NUMBER:       | 2005:1328488 HCAPLUS   |
| П   | DOCUMENT NUMBER:        | 144:51894  |
| I   | TITLE:                  | One-pot process for the preparation of nateglinide                       |
| Н   | INVENTOR(S):            | Kankan, Rajendra Narayanrao; Rao, Dharmaraj                              |
|     |                         | Ramachandra; Singh, Manjinder; Birari, Dilip Ramdas                      |
| ы   | PATENT ASSIGNEE (S):    | Cipla Limited, India; Wain, Christopher Paul                             |
| S   | SOURCE:                 | PCT Int. Appl., 32 pp.   |
|     |                         | CODEN: PIXXD2  |
| Ц   | DOCUMENT TYPE:          | Patent   |
| Н   | LANGUAGE:               | English  |
|     | FAMILY ACC. NUM. COUNT: |  |
| 114 | PATENT INFORMATION:     |  |

| PATENT NO.       | NO.        |      |        | KIND   |         | DATE                                 |      | ~            | APPLI        | CAT        | APPLICATION NO.         | <u>.</u> |        | ä       | DATE        |     |  |
|------------------|------------|------|--------|--------|---------|--------------------------------------|------|--------------|--------------|------------|-------------------------|----------|--------|---------|-------------|-----|--|
| WO 2005121071    | 1210       | 11   |        | F      |         | 20051222                             | 222  | , ,,,        | WO 2005-GB22 | 0.5-0      | WO 2005-GB2267          | -        |        | i X     | 20050608    | 808 |  |
| 33               | ΑĒ,        | AG,  | AĽ,    | AM,    | AT,     | AU,                                  | A2,  | BA,          | BB,          | BG,        | BR,                     | BW,      |        | , Z8    | BZ, CA, CH, | CH, |  |
|                  | S,         |      | CR,    | G<br>G | ,<br>22 | DE,                                  | DK,  | Ω,           | DZ,          | ည <u>ှ</u> | EE,                     | EG,      | ES,    | FI,     | g,          | GD, |  |
|                  | GE,        |      | ₽<br>₩ | HR,    | HO,     | īΩ,                                  | II,  | Ľ,           | IS,          | 닭,         | Ä                       | KG,      |        | КР,     | ₩,          | Κ2, |  |
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|                  | NG,        |      | NO,    | NZ,    | ĕ,      | PG,                                  | PH,  | P.           | PT,          | 80,        | RU,                     | SC,      |        | SE,     | SG,         | SK, |  |
|                  | SI,        |      | SY,    | TJ,    | Ę       | II,                                  | TR,  | ŢŢ,          | TZ,          | ď,         | ug,                     | us,      |        | VC,     | ₹           | ΥŪ, |  |
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|                  | AZ,        |      | KG,    | K2,    | ð       | RU,                                  | TJ,  | Ŧ,           | AT,          | BE,        | BG,                     | Ğ,       | ;      | CZ,     | E,          | DK, |  |
|                  | EE,        |      | FI,    | Ε,     | В,      | g,                                   | HO,  | E,           | ıs,          | ij,        | Ľľ,                     | Ľ,       | Ř,     | Ę       | PĽ,         | PT, |  |
|                  | МО,        |      | SI,    | SK,    | TR,     | BF,                                  | ВЈ,  | <del>ე</del> | g,           | r,         | Ŗ,                      | G,       | ₹<br>8 | ĝ       | ₹,          | Æ,  |  |
|                  | Ä,         |      | SN,    | ŢĎ,    | 13      |                                      |      |              |              |            |                         |          |        |         |             |     |  |
| AU 2005          | 2005252002 | 02   |        | A      |         | 2005                                 | 222  |              | N 20         | 05-2       | 5200                    | 2        |        | 7       | 0020        | 809 |  |
| CA 2570041       | 041        |      |        | AI     |         | 20051222                             | 222  |              | .A 20        | 05-2       | 5700                    | 41       |        | 7       | 20050608    | 809 |  |
| EP 1765769       | 169        |      |        | Al     |         | 20070328                             | 328  |              | 3P 20        | 05-7       | EP 2005-750279          | ق        |        | ×       | 20050608    | 808 |  |
| <br>             | AT,        | BE,  | BG,    | CH,    | ն՝      | CY, CZ, DE,                          | DE,  | Ķ,           | EE,          | ES,        | DK, EE, ES, FI, FR, GB, | E,       | 8      | я,<br>, | GR, HU, IE, | IE, |  |
|                  | IS,        | II,  | Ľ,     | Ľ,     | 3       | Ř,                                   | NI,  | PL,          | ΡΤ,          | RO,        | SE,                     | SI,      | SK,    | TR      |             |     |  |
| PRIORITY APPLN.  |            | INFO |        |        |         |                                      |      | _            | 3B 20        | 04-        | GB 2004-13084           |          | _      |         | 040         | 111 |  |
|                  | -          |      |        |        |         |                                      |      | _            | 80 20        | 05-0       | WO 2005-GB2267          |          |        | 2       | 7 20050608  | 808 |  |
| OTHER SOURCE (S) | (8)        |      |        | 200    | FAC     | CASREACT 144-51894: MARPAT 144-51894 | 1.51 | . 76         | MAR          | . TA       | 44.                     | 11894    |        |         |             |     |  |

? SOURCE(5): A now-pot process for the preparation of nateglinide is presented which comprises amidation of a C1-4 alkyl ester of D-phenylalanine, either as the free base or in salt form (typically the hydrochloride), OTHER AB P

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Page 7

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

14 HCAPLUS COPYRIGHT 2007 ACS ON STN
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156:2312 with trans-4-isopropylcyclohexanecarboxylic acid or its acid halides to obtain a Cl-4 alkyl ester of nateglinide, preferably the Me ester of nateglinide, followed by alkali (e.g., NaOH) saponification and acidification (e.g., HCl) to yield nateglinide (m.p. 128-131°).

REFERENCE COUNT:

6 RECORD. ALL CITATIONS AVAILABLE FOR THIS RECORD. 15 ANSWER 3 OF 14 H ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: PATENT ASSIGNEE(S): INVENTOR (S): SOURCE:

LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE:

| PATI     | PATENT NO.    | <i>.</i> : |      |     | KIND | _        | DATE    |     | 1   | APPLICATION NO. | PPLICATION   | NO    | ç.       |     | ā       | DATE     | }   |
|----------|---------------|------------|------|-----|------|----------|---------|-----|-----|-----------------|--------------|-------|----------|-----|---------|----------|-----|
| 0.0      | WO 2005113485 | 348        | 1 5  |     | 2    | ,        | 2005    | 201 |     | WO 2005-US17664 | 05-1         | 18176 | 564      |     | 7       | 20050520 | 50  |
|          |               | Æ,         | AG,  | Ą,  | Ä,   | AT,      | AU, AZ, | AZ, | BA, | BB,             | ВЗ,          | BR,   | BW,      | BY, | В2,     | ą        | G,  |
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|          | U             | 띥,         | GH,  | Ę   | HR,  | ĦO,      | ID,     | ľ,  | Ľ,  | IS,             | Ę,           | ₽,    | KG,      | ₩,  | ΚP,     | Ж,       | ΚΖ, |
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|          | ~             | Ğ,         | NI,  | NO. | NZ,  | ĕ        | PG.     | PH, | PI, | PT,             | ЖО,          | RU,   | sc,      | SD, | SE,     | SG,      | SK, |
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|          | 2             | Ä,         | ZM,  | ΜZ  |      |          |         |     |     |                 |              |       |          |     |         |          |     |
|          | RW: E         | 35.        | GH,  | ₹   | ₽,   | ĽŠ,      | ₹       | M2, | Ä,  | SD,             | SI,          | SZ,   | TZ,      | ug, | ZM,     | ZW,      | Æ,  |
|          | et.           | ,2,        | BY,  | ĸĠ, | K2,  | Ď        | RU,     | TJ, | IM, | AT,             | BE,          | BG,   | CH,      | CX, | ,<br>22 | Œ,       | DK, |
|          | ш             | E)         | ES,  | FI, | Ά,   | g,       | GR,     | В,  | Ξ,  | IS,             | II,          | Ľ,    | ĽŪ,      | Ã,  | Ä,      | PL,      | PT, |
|          | 41,           | ò          | SE,  | SI, | SK,  | TR,      | BF,     | ВЈ, | GF, | ც               | CI,          | સં    | g,       | ĞN, | ĝ       | ĞW,      | MI, |
|          | 2             |            | NE,  | SN, | ŢĎ,  | ភិ       |         |     |     |                 |              |       |          |     |         |          |     |
| PRIORITY | APPLN.        | _          | NFO. |     |      |          |         |     | _   | JS 2(           | 04-5         | 37268 | 39P      | ш   | 2       | 0405     | 20  |
|          |               |            |      |     |      |          |         |     | _   | us 2(           | 2004-586431P | 864   | 31P      | 114 | ×       | 20040708 | 80, |
|          |               |            |      |     |      |          |         |     | _   | JS 20           | 905-6        | 3446] | 14P      |     | 5       | 00501    | 18  |

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A process for preparing nateglinide Form B comprises dissolving nateglinide (I) in a solvent and adding the solution, at temps. of  $40+45^\circ$ C, to a hydrocarbon liquid that is at temps. of  $40-45^\circ$ C. Then, water is added and the mixture is allowed to cool, producing crystals of nateglinide ΑB

Form B.

| 14 HCAPIUS COPYRIGHT 2007 ACS on STN: 2005:1240947 HCAPIUS 144:11582 | Process for the preparation of pol<br>forms of nateglinide ammonium salt | (S): Wizel, Shlomit; Frenkel, Gustavo; Gome, Boaz SSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva |         | TYPE:<br>C. NUM. COUNT:<br>FORMATION:                                   | . KIND DATE APPLICATION NO. | 2005110972 A1 20051124 WO 2005-US16343 20050509 | G, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, | CR, CU, CZ, DE, DK, DM, DZ, EC,<br>GM, HR, HU, ID, IL, IN, IS, JP, | IK, IR, IS, IT, IU, IV, MA, MD, MG, MK, MN, MW, MX, MZ, | NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, | ZA, ZM, ZW | RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZM, AM, 7 TZ, UG, ZM, CH, CY, CY, TY, AM, TY, TM, TY, DE, DC, CH, CY, CY, TY, DK | ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, | SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, | , NE, SN, TU, TG | 102                       | 6339 Al ZUU6U3I/ EF ZUU3-148381<br>nm nn cu nn nn nr nr en ch ch tm 11 111 N1 en | SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, | BA, HR, IS, YU 2007-0418 CN 2005-80014509 2005050509 | INFO:: CONTAINS ON 2004-569047P P WO 2005-US16543 W | hyperglycemic polymorphic crystalline forms of nateglinid | t are prepared  1 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS  5 COUNT: DEFINED ALL CITEMATIONS ANALIBRE IN THE DE FROMET | KECUND, ALL CIMITONS AVALLABLE IN THE KE CONTAIN | 14 HCAP                          | 143:7982         | Process for the preparation of the crystalline B-form nateginide from D-phenylalanine methyl ester and trans-d-isomeronylor) phesamecarboxylic acid | Videno', Enrico; Pizzati, Enrica; Lanfi<br>Wolfeni Bensto: Landonio Ernesto | A.M.S.A. Anonima    | Eur. Pat. Appl., 32 pp. | Patent         |
|--|--|---|---------|---|-----------------------------|---|--|--|---|---|------------|--|---|---|------------------|---------------------------|--|---|--|---|---|--|--|----------------------------------|------------------|---|---|---------------------|-------------------------|----------------|
| L5 ANSWER 4 OF<br>ACCESSION NUMBER:<br>DOCUMENT NUMBER:              | TITLE:   | INVENTOR(S):<br>PATENT ASSIGNEE(S)  | SOURCE: | DOCUMENT TYPE:<br>LANGUAGE:<br>FAMILY ACC. NUM. C<br>PATENT INFORMATION | PATENT NO.                  | WO 20051109                                     | W: AE,   | S. G.  | ic,   | NG,   |            |  | EE,   | RO,   |                  | CA 2563793<br>US 20060041 | 16563  |   | BA,  | CN 1930331<br>PRIORITY APPLN.                       | AB Anti-hyperg  | sait are pr<br>REFERENCE COUNT:  |  | L5 ANSWER 5 OF ACCESSION NUMBER: | DOCUMENT NUMBER: | TITLE:  | INVENTOR(S):  | PATENT ASSIGNEE(S): | SOURCE:                 | DOCUMENT TYPE: |

Page 9 searched 5/2/07

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

| DATE            | SE, MC, PT, HU, SK, 20031126 20031126 20031126 20031126 Am ester, or a acyl acyl nc it in a water and alkali water and alkali water for a lear and alkali it isolating the step (Ia), and f nateglinide;   | step (II) is a<br>ABLE FOR THIS<br>THE RE FORMAT  | idiabetics<br>Kaixian<br>Academy of<br>Shu, 26 pp.   | DATE            | 20030124<br>20030124  |
|-----------------|--|---|--|-----------------|---|
| APPLICATION NO. | EP 2003-27114  B, GR, IT, IL, IU, NL, Y, AL, TR, BG, CZ, EE, AT 2003-27114  EP 2003-27114  Aglinide comprises: (I) equene D-phenylalanine ecarboxylic acid and an obtain the nateglinide Me ester and redissolvi tion; (II) addition of ing from step (I) witho ing from step (I) witho ing the solution of ining the alkali salt o o the aqueous phase com  | , wherein the organic solvent employed in step (II) is solvent.  3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAN | LUS COPYRIGHT 2007 ACS on STN 2005:414565 HCAPLUS 142:4821315 Foregration of alanine derivative as antidiabetics Yang, Yushe; Tang, Lei; Ji, Ruyun; Chen, Kaixian Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China Faming Zhuani Shenqing Gongkai Shuomingshu, 26 pp CODEN: CNXXEV Patent Chinese | APPLICATION NO. | A 20030723 CN 2003-115160<br>CN 2003-115160<br>CASREACT 142:482315; MARPAT 142:482315 |
| KIND DATE       | Al 20050601 Bl 2006127 DE, DK, ES, FR, G IV, FI, RO, MK, C T 20070115 CASREACT 143:7982 creparation of nate organic solvent borpropylcyclohexan. Idinimazole, to the nateglinide nt to give a solu cution mixture com int to give a solu cution mixture com int con in mixture com int con int contant c | wherein the orgasolvent. 3 THERE ARE TECORD. ALM  | HCAPLUS COPYRIGHT 2007 ACS on 2005:414565 HCAPLUS 142:482315 Ptg.482315 Preparation of alamine derivancy, Yushe; Tang, Lei; Ji, Shanghai Institute of Pharm Sciences, Peop. Rep. China Faming Zhuanli Shenqing Gorodon: CNXEV Patent Chinese T: 1  | KIND DATE       | A 20030723<br>CASREACT 142:4823   |
| PATENT NO.      | EP 1535900 EP 1535900 R: TX, BE, CH, AT 349418 PRIORITY APPLAN. INFO.: OTHER SOURCE(S): AB A process for the praction in a first salt, and trans-4-is chloride, or carbony optionally isolating second organic solve hydroxide to the rean arteglinide Me ester separation of the aquit.   | obtain nateglinide<br>water non-miscible<br>FERENCE COUNT:  | LS ANSWER 6 OF 14 HCAP ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:   | PATENT NO.      | CN 143197 PRICRITY APPLM, INFO.: OTHER SOURCE(S):                                     |

Page 10 searched 5/2/07

AB Alanine deriva: I (RI = 2-(1-indoly1)ethyl, 2-[N-(2-benzoxazoly1)-N-methyl-2-ph-nyl-4-oxazoly1)ethyl, 4-[N-methyl-1] aminoethyl, 2-(N-methyl-2-phenyl-4-oxazoly1)ethyl, 4-trifluoromethylbenzyl, benzyl; R2 = H, alkyl) is prepared by condensation reaction of trans-4- is prepared by condensation reaction of trans-4- is prepared by condensation reaction of trans-4- benzyl; R2 b-tyrosine Me ester in inert solvent to obtain 3-(4-hydroxyphenyl)-2- (trans-isopropylcyclohexylcaroxamido)propanoic acid Me ester [II). Mitsunobu reaction with aromatic alc., and then hydrolysis with inorg. base solution The method may be prepared by (I) etherification of II with alide in alkaline medium; (2) hydrolysis of II; or (3) condensation reaction with 2-iluoropyridine, and hydrolysis with base. The alanine derivative and its salt may be used to prepare the medical prepare. for treating type II diabetes mellitus.

L5 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:5980 HCAPLUS
DOCUMENT NUMBER: 142:141289
TITLE: Crystalline form of nateglinide
Crystalline form of nateglinide
Frenkel, Gustavo; Gome, Boaz; Wizel, Shlomit
PATENT ASSIGNEE(S): Israel
SOUNCE: Ser. No. 622,905.
CODEN: USXXCO
DOCUMENT TYPE: Patent
Patent
Patent
Patent
SOUNCE: CODEN: USXXCO
DOCUMENT TYPE: Patent

COUNENT TYPE:
Patent
LANGUAGE: Patent
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

BZ, CA, CH, FI, GB, GD, KR, KZ, LC, MZ, NA, NI 20040113 SE, MC, PT, HU, SK 20040113 20040113 20030718 20030123 20031224 DATE BY, ES, KP, EP 2004-701826 GB, GR, IT, LI, LU, N CY, AL, TR, BG, CZ, E CX 2004-80005672 US 2006-516363 US 2003-442109P US 2003-746697 US 2003-622905 CA 2004-2513753 WO 2004-US839 APPLICATION NO. Ř BA, BB, 1 DM, DZ, IN, IS, MD, MG, 20040916 20040812 20040812 20040812 ES, FR, RO, MK, 20060920 20070104 ALK, 20050120 20050309 DATE AT, CZ, HU, KIND A1 A1 A1, LT, LT, LY, LV, ¥.8.8.3 £, ; US 2007004804 PRIORITY APPLN. INFO.: AE, AG, GR, GO, LK, LR, AT, BE, IE, SI, US 2005014836 US 2004181089 CA 2513753 WO 2004067496 WO 2004067496 LK, EP 1511717 CN 1835912 US 20070048 PATENT NO. ж ж

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

| 20030224     | 20030616     | 20030718    | 20020718     | 20020925     | 20020926     | 20021105     | 20021210     | 20021212     | 20030718    | 20030718     | 20031023    | 20031224    | 20040113   |
|--------------|--------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|-------------|--------------|-------------|-------------|------------|
| ᇝ            | Д            | A2          | д            | Δ            | а            | Д            | д            | Ы            | A1          | ď            | Ø           | Æ           | 3          |
| 2003-449791P | 2003-479016P | 2003-622905 | 2002-396904P | 2002-413622P | 2002-414199P | 2002-423750P | 2002-432093P | 2002-432962P | 2003-622999 | 2003-0522375 | 2003-693166 | 2003-746697 | 2004-US839 |
| ns           | Sn           | Sn          | OS           | SD           | ns           | ns           | ns           | Sn           | US          | OM<br>MO     | US          | US          | WO         |
|              |              |             |              |              |              |              |              |              |             |              |             |             |            |
|              |              |             |              |              |              |              |              |              |             |              |             |             |            |

AB Crystalline forms of nateglinide and processes for their preparation, as well as

pharmaceutical formulations containing them and methods of administration are provided. A process for preparing crystalline form of nateglinide comprises

the steps of(a) preparing a solution of nateglinide in Et acetate, (b) seeding the solution with nateglinide crystals, and (c) recovering the crystalline form as

precipitate The nateglinide obtained is more than about 99% pure. For example,

nateglinide (5 g) was dissolved in acetonitrile, acetone, or Et acetate at nateglinide (5 g) was dissolved in acetonitrile, acetone, or Et acetate at about 55° in over about 15 min until a clear solution was obtained.

The solvent was removed to dryness by evaporation at about 55°/20 to 30 mmig to give dry nateglinide crystalline Form B. Also, nateglinide Form Z was prepared by treating 7.73 g of D-phenylalanine (PheOH) with 185 mL (3.5 equiv) of 3.5% NaOH at room temperature to afford a clear solution of the corresponding Na-salt. A solution of neat trans-4 sisopropylcyclobranecarboxyl chloride (IPCHAC, 9.02 g, 1.01 equiv) was added to the solution of Phe-OH obtained above, over 3 min, while stirring at room temperature The rest of the IPCHAC in the funnel was washed with toluene (I mL) and added. The resulting mixture was stirred for 1 h, and was treated with 10% HCl (32 mL) to adjust the pH to 3, while stirring. The mixture was stirred for 1 h, and was stirred for 1 h, and was stirred for 1 h, and was leaved with water (200 mL) and sucked well to afford 33.3 g of the moist product, which lost weight after drying at 78°/2.2 mbar (Assay 98.4%, purity >99%, yield 86%).

LS ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:55192 HCAPLUS
DOCUMENT NUMBER: 142:156316
TITLE: A saponification and neutralization process for the preparation of chirally pure nateglinide from its lower alkyl esters and nateglinide from its lower alkyl esters and nateglinide from its lower alkyl esters and nateglinide polymorphic crystalline modifications
INVENTOR(S): Gazday Mania; Gizur, Tibor; Hegedus, Bela; Szemzo, Attila; Tarkanyl, Gabor; Toerley, Jozsef; Babjak, Monika
PATENT ASSIGNEE(S): Richer Gedeon Vegyeszeti Gyar Rt., Hung. CODEN: PIXXD2
DOCUMENT TYPE: Richer Gedeon Vegyeszeti Gyar Rt., Hung. PATENT ASSIGNEE (S): Richer Gedeon Vegyeszeti Gyar Rt., Hung. PATENT ASSIGNEE (S): Richer Gedeon Vegyeszeti Gyar Rt., Hung. PATENT ASSIGNEE(S): Richer Gedeon Vegyeszeti Gyar Rt., Hung. PATENT ASSIGNEE(S): Richer Gedeon Vegyeszeti Gyar Rt., Hung. PATENT ANCUMAGE: Richer Ratent Batent Bat

Page 12 searched 5/2/07

Page 11 . searched 5/2/07

|                 |               |                |                 |                 |                   |                 |                 |             |                 |             |                 |     |              |                |                 |             |                |                        |              |                     | i.   |  |   |  |  |   |   |
|-----------------|---------------|----------------|-----------------|-----------------|-------------------|-----------------|-----------------|-------------|-----------------|-------------|-----------------|-----|--------------|----------------|-----------------|-------------|----------------|------------------------|--------------|---------------------|--|--|---|--|--|---|---|
| DATE            | 20040708      | (, BZ, CA, CH, | FI, GB,         | KR, KZ,         | 4, MZ, NA, NI,    | SK, SL,         | ZA, ZM,         | ZM, ZW,     | CZ, DE,         | PT,         | Œ,              |     | 20030710     | 20040708       | NL, SE, MC, PT, | PL, SK, HR  | 20060515       | A 20030710             | W 20040708   |                     | a nateglinide lowe   | odium hydroxide)   |   | ed as is the   | steglinide.  | IN THE RE FORMAT  |   |
| APPLICATION NO. | WO 2004-HU73  | BR,            | DZ, EC, EE, EG, | IS, JP, KE, KG, | MK, MN, MW,       | RU, SC, SD, SE, | US, UZ, VC, VN, | SD, SL, SZ, | AT, BE, BG, CH, | LU, MC, NL, | CM, GA, GN, GO, |     | HU 2003-2174 | EP 2004-743732 |                 |             | US 2006-564017 | HU 2003-2174           | WO 2004-HU73 | 3316                | The preparation of chirally pure nateglinide by treating a nateglinide lower | alkyl ester (e.g., Me ester) with an alkali base (e.g., sodium hydroxide | to yield an alkali salt and neutralizing liberating the | salt by addition of an acid (e.g., aqueous HCl) is described as is the | preparation of polymorphic crystalline modifications of nateglinide. | IMEKE AKE 0 CITED KEFEKENCES AVAILABLE FOR IMIS<br>RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT |   |
| KIND DATE       |               | AM, AT, AU,    | CU, CZ, DE,     | HR, HU, ID,     | ; IT, IU, IV, MA, | PG, PH, PL,     | TR, TT, TZ,     | KE, LS, MW, | KZ, MD, RU,     | FR, GB, GR, | BF, BJ, CF,     |     | A2 20050728  |                | DE,             |             | A1             |                        |              | CASREACT 142:156316 | chirally pure nat  | Me ester) with an  | salt and neutrali                                       | f an acid (e.g., a   | ymorphic crystalli   | RECORD, AI  | ! |
| PATENT NO.      | WO 2005005373 | AG,            | °,              | GH,             | IK, LR, LS,       | NZ,             | Ĭ,              | GH,         | BY,             | ES,         | SK,             | TD, | HU 200302174 | EP 1651591     |                 | IE, SI, LT, |                | PRIORITY APPLN. INFO.: |              | OTHER SOURCE(S):    | AB The preparation of  | alkyl ester (e.g.,   | to yield an alkali                                      | salt by addition o   | preparation of pol   | KEFERENCE COONI:  |   |

| PATENT  | NO.        |      |     | KIND | _   | DATE  |          | - | APPLICATION | ICAT |             | NO. |     | 2   | PATE     |                |
|---------|------------|------|-----|------|-----|-------|----------|---|-------------|------|-------------|-----|-----|-----|----------|----------------|
|         | -          | 1    |     | į    |     | į     | 1        |   |             | -    | -           |     | •   | i   | į        | ł              |
| WO 2004 | 2004018408 | 80   |     | A1   |     | 20041 | 0304     |   | WO 2        | 003- | 2003-IB3270 | 20  |     | ŏ   | 20030812 | 812            |
| WO 2004 | 2004018408 | 80   |     | A8   |     | 2005  | 20050310 |   |             |      |             |     |     |     |          |                |
| 3       | AE,        | ÅĞ,  |     | AM,  | AT, |       | AZ,      |   | BB,         | BG,  | BR,         | BY, | В2, | ð   | E,       | $\overline{S}$ |
|         | 8          | g,   |     | CZ,  | E,  |       | Ξ,       |   | EC.         | EE,  | ES,         | FI, | GB, | 9   | GE,      | 픙              |
|         | Æ          | HR,  |     | ID,  | II, |       | IS,      |   | Ā           | KG,  | KP,         | Ж,  | KZ, | Ľ,  | ĽĶ,      | Ľ              |
|         | LS,        | ĽĽ,  | ĽŪ, | Ľ    | Ę   |       | WG,      | Ř | Ā           | ¥    | Ř           | MZ, | NI, | Š,  | NZ,      | §              |
|         | PG,        | PH,  |     | PT   | 80, |       | sc,      |   | SE,         | SG,  | SK,         | SI, | SX, | ŢĴ, | Ĕ,       | Į,             |
|         | TR,        | TI,  |     | UA,  | ŋĠ, |       | UZ,      |   | Š           | χΩ   | ZA,         | ZM, | ΜZ  |     |          |                |
| RW:     | GH,        | Æ    |     | I.S. | M.  |       | SD,      |   | 25          | TZ,  | ug,         | ZW, | ZW, | AM, | A2,      | BY             |
|         | KG         | KZ,  |     | RU,  | ₹,  |       | AT,      |   | BG,         | CH,  | ζ,          | CZ, | Œ,  | Ķ,  | EE,      | S              |
|         | FI,        | ۳    |     | GR,  | HU, |       | II,      |   | Ä           | NI,  | PT,         | ЖО, | SE, | SI, | SK,      | TR             |
|         | BF         | B.I. |     | S    | H   |       | ď        | _ | 9           | 35   | Ä           | Ĕ   | Ä   | SN  | TD.      | Ę              |

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### 10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

| 20020826 20030812 A 20020826 W 20020826 745 w 20030812 carboxylic acid with ence of a base at with an aqueous cows the chloroformate in AVALIABLE FOR THIS LE IN THE RE FORMAT  | its<br>itzky, Ben-zion;<br>Israel; Teva<br>°   | DATE  20030703 CA, CH, CN, CH, CN, CD, CE, CH, LR, LL, LR, LL, LR, LL, LR, LR, ET, ES, ES, ES, ES, ES, ES, ES, ES, EN, TD, TG, TD, TD, TG, TD, TD, TD, TD, TD, TD, TD, TD, TD, TD |
|---|--|---|
| NEO. IN 2002-MU773  A1 20040605 IN 2002-MU773  NEO.:  CASREACT 140:199745, WARPAT 140:199745  REOCORDATE IN A RECORD IN 199745  MARPAT 140:199745  MARPAT 140:199745 | 14 HCAPLUS COPYRIGHT 2007 ACS on STN 2004:41431 HCAPLUS 140:94292 Process for preparing nateglinide and intermediates Yahalomi, Ront; Shapiro, Evgeny; Dol Gozlan, Yigael Gozlan, Yigael Teva Pharmaceutical Industries Ltd., Pharmaceuticals Usa, Inc. Pharmaceuticals Usa, Inc. CODEN: PIXXD2 Patent English English | KIND DATE  A1 20040115 WO 2003-US21238  A2 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BE, CR, CU, CZ, DE, DK, DZ, EC, EE, ES, FI, GB, IT, IU, ID, IL, IN, IS, DY, KE, KG, KF, KR, KZ, LT, LU, LU, NA, MO, MO, MO, MO, MO, MO, MO, MO, MO, MO   |
| IN 2002MU0077 AU 2003263386 PRIORITY APPLM. IN OTHER SOURCE(S): AB N-{(trans-4-i)} was prepared an alkyl chlc -20 to 30°C alkali salt synthesis of synthesis of acctone (97% REFERENCE COUNT:   | L5 ANSWER 10 OF 1 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. CO PATENT INFORMATION:  | PATENT NO.  WO 20040055  WO 20040055  EAGLE IS TRWI GHING THE FILE FILE FILE FILE FILE FILE FILE FIL  |

Page 14 searched 5/2/07

P 20021105

US 2002-423750P

| IP P 20021210   | P 20021212        | P 20030123      | .P P 20030224   | 5P P 20030616   | 18 W 20030703     | A1 20030718    |                                     | s converting  | acid chloride by  | organic amide and  | the acid  | free of a co-solvent.   | S AVAILABLE FOR THIS   | TABLE IN THE RE FORMAT                        |
|-----------------|-------------------|-----------------|-----------------|-----------------|-------------------|----------------|-------------------------------------|---|---|--|---|---|--|---|
| US 2002-432093P | . US 2002-432962P | US 2003-442109P | US 2003-449791P | US 2003-479016P | . WO 2003-US21238 | US 2003-622999 | OTHER SOURCE(S): CASREACT 140:94292 | AB A process for the preparation of nateglinide involves converting | trans-4-isopropylcyclohexanecarboxylic acid into the acid chloride by | reaction with thionyl chloride in the presence of an organic amide and | acylation of a suitable salt of D-phenylalanine with the acid | chloride in a single or two phase system or in water free of a co-solvent | REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS | FEMOLO SE SHE NI SIGRIFUL SNOTHWELD LIK GOOGS |

L5 ANSWER 11 OF 14 HCAPLUS COPPRIGHT 2007 ACS on STN ACCESSION NUMBER: 2003:737716 HCAPLUS DOCUMENT NUMBER: 139:230996
TITLE: Preparation and properties of nateglinide salts inventoR(S): Preparation and properties of nateglinide salts inventoR(S): Parker, David John: De La Cruz, Marilyn PATENT ASSIGNEE(S): Novartis Ag, Switz.; Novartis Pharma Gmbh SOURCE: POCUMENT TYPE: Patent LANGUAGE: Patent

| PA.     | PATENT NO.      |       |        | KIND |     | DATE     |      | -   | APPLICATION NO.     | CATI      | NO           | ō.       |     | ā i    | DATE     | . } |
|---------|-----------------|-------|--------|------|-----|----------|------|-----|---------------------|-----------|--------------|----------|-----|--------|----------|-----|
| . W     | WO 2003076393   | 393   |        | ¥    |     | 20030918 | 918  |     | WO 2003-EP2447      | 03-E      | :P244        | 1        |     | ×      | 20030310 | 310 |
|         | W: AE,          |       | AI,    | Æ,   | AT, | AU,      | AZ,  | BA, | BB,                 | BG,       | BR,          | ВХ,      | BZ, | ð      |          | CS, |
|         | 8               |       | G<br>G | ζ2,  | DE, | Ŗ,       | Ď,   | DZ, | EC,                 | EE,       | ES,          | EI,      | GB, | g<br>B |          | GH, |
|         | HR,             | , HU, | ID,    | II,  | ï,  | ıs,      | JP,  | Ä   | KG,                 | К₽,       | Ж,           | Κ2,      | ĽĊ, | ĽĶ,    | ĽĮ,      | ĽŪ, |
|         | Ľ               |       | ě      | Ă,   | Š   | Ř        | NI,  | Š,  | NZ,                 | ₽,        | PH,          | P.L.,    | PT, | 8      |          | sc, |
|         | SE,             |       | SK,    | ŦJ,  | Ĕ,  | IN,      | TR,  | ŢŢ, | ďA,                 | ns,       | UZ,          | VC,      | Š   | χΩ     |          | ΜZ  |
|         | RW: AM          |       | BY,    | KĞ,  | KZ, | ð        | RU,  | 13, | Ţ,                  | AT,       | BE,          | BG,      | CH, | ζ,     |          | Œ,  |
|         | DK,             |       | ES,    | FI,  | 톴,  | GB,      | GR,  | ĦŪ, | ΞĚ,                 | ij        | ĽQ,          | Ř,       | NT, | Д,     |          | SE, |
|         | SI              |       | TR     |      |     |          |      |     |                     |           |              |          |     |        |          |     |
| 5       | 24785           |       |        | Al   |     | 20030918 | 9160 | _   | GA 20               | 303-2     | 2003-2478599 | 669      |     | ñ      | 20030310 | 310 |
| AU      | 2003214112      | 112   |        | A1   | •   | 20030922 | 1922 | *   | N 20                | 3-500     | 1411         | 2        |     | ñ      | 20030310 | 310 |
| EP      | 1483232         |       |        | A1   | •   | 20041208 | 1208 | ш   | EP 2003-709769      | 03-7      | 1097         | 65       |     | Ñ      | 20030310 | 310 |
|         | R: AT           | , BE, | CH,    | DE,  | Ŗ,  | ES, FR,  | Ŧ,   | GB, | GB, GR, IT, LI, LU, | II,       | Π,           | E,       | NĽ, | SE,    | SE, MC,  | PT, |
|         | IE,             |       | Ľ,     | Ľ,   | EI, | 80,      | Ř    | ĊĬ, | ¥,                  | TR,       | BG,          | C2,      | 띮   | ΉΩ     | SK       |     |
| BR      | 2003            | 316   |        | ď    |     | 20041    | 1228 |     | BR 20               | 2003-8316 | 3316         |          |     | 7      | 20030310 | 310 |
| JP      | 2005519949      | 949   |        | e    | •   | 20050707 | 7070 | ٠,  | JP 20               | 303-5     | 2003-574615  | 5        |     | ~      | 20030310 | 310 |
| S       | 1642904         |       |        | ď    |     | 20050720 | 720  | Ö   | CN 20               | 93-6      | 2003-805803  | <u>ب</u> |     | ~      | 20030310 | 310 |
| ns      | 2005234129      | 129   |        | A1   | •   | 20051020 | 1020 | ۰   |                     | 04-5      | 2004-507255  | 55       |     | 5      | 20040928 | 928 |
| PRIORIT | PRIORITY APPLN. | INFO. | •:     |      |     |          |      | ٥   | US 20               | 302-3     | 2002-363178P | 18P      |     | P 2    | 0020311  | 311 |

WO 2003-EP2447 W 20030310

The invention relates to salts of nateglinide having specified properties (m.ps., solubilities, X-ray diffraction patterns) for use in pharmaceutical compons. for preventing or treating diabetes, cardiovascular diseases, etc. Nateglinide Na, K, Ca, Mg, N-methyl-D-glucamine, TRIS, lysine, and ammonium salts were prepared and their properties

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10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

REFERENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LS ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:
DOCUMENT NUMBER:
136:325420
TITLE:
DOCUMENT NUMBER:
11 Inkers, and a nitrate ester
11 Inkers, and a nitrate ester
12 SOURCE:
13 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ACS OF STN

ACCESSION NUMBER:
136:325420
TITLE:

20011009 20011009 20011009 NL, SE, MC, PT, CZ, DM, DZ, LK, LR, LT, TR, TT, UA, TM EB, CH, CY, SE, TR, BF, TD, TG 20011009 20030411 20001012 20011009 20011009 CU, IC, SK, PT, SN, GB, GR, IT, LI, LU, N CY, AL, TR 5 JP 2002-534256 5 US 2003-398511 IT 2000-MIZ201 WO 2001-EP11665 CA 2001-2425655 AU 2002-14006 EP 2001-982414 CN, CR, KP, KR, SG, SI, MD, RU, UG, ZW, MC, NI, WO 2001-EP11665 APPLICATION NO. MARPAT 136:325420 GR, KA, DK, FI, KIND
A2
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A4 ; ; SE KK KK US 2004023890 PRIORITY APPLN. INFO.: R: AT, BE, C IE, SI, I JP 2004511456 W: AE, AG, EE, GD, LV, MA, US, UZ, RW: GH, GM, DE, DK, BJ, CF, IT 2000MI2201 IT 1319201 CA 2425655 AU 200214006 EP 1324974 WO 2002030867 WO 2002030867 2000MI2201 OTHER SOURCE(S): GI PATENT NO.

OMO2

AB Useful for the treatment of diabetes, particularly type 2, are compds. or salts thereof, having the following general formula

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Page 16 searched 5/2/07

A-(B)n-(C)m-NO2 [I; wherein A = radical of a drug having an antiinflammatory or analgesic activity; B = bivalent linking group wherein the precursor must meet certain tests described in the application; C = another defined bivalent linking group; n and m = 0 or 1, provided that (n + m) = 1 or 2]. I can be used in conjunction with other antidiabetic drugs; particularly lusulin. I increase the direct antidiabetic effect of insulin, and reduce complications of diabetes, particularly vascular diseases, retinopathies, neuropathies, etc. The values of n and m, i.e., the presence or absence of bivalent linkers B and C, alone or in combination, are based on performance of the precursors of the linkers in certain tests (no data). These tests are designated as follows: (test 4A): inhibition by > 15 of hemolysis of rat erythrocytes induced by cumene hydroperoxide; (test 5): inhibition of radical production by ≥ 50% in the oxidative degradation of . desoxyribose in aqueous Fe2+(M4)/S(SO4)Z(thiobarbituric acid solution; and (test 4): inhibition by > 15 of hemolysis of rat erythrocytes induced by certificate distribution for inhibition by > 50% of DPPH-induced radical production in MeOH solution for inhibition by > 50% in the oxidative degradation of . desoxyribose in aqueous certylsalicylic acid chloride was esterified with 3-(Mydroxymethyl)phenol (80%), followed by nitation of the resultant Ph ester with HNO3/H2SO4 (82%), to give invention compound II. which is thus the 3- (nitroxymethyl)phenyl ester of appirin. When tested on isolated aorta from insulin-resistant rats, compound II at a concentration of 10-4 M gave vasculaxation, relative to non-insulin-resistant controls. This effect was unchanged by the presence or absence of the irreversible NO synthetiase inhibitor INNA. In contrast, both Na nitroprussiate and the indomethacin analog of II, known NO donors, were inactive, and the antidiabetic drug metformin was inactivated by LNNA.

use as hypoglycemic agents
Toyoshima, Shigeshi; Seto, Yoshiko; Shinkai, Hisashi;
Toi, Koji; Kumashiro, Izumi
Ajinomoto Co., Inc., Japan
CODEN: EPLX Appl., 25 pp. Correction of: 106:19047
Preparation of D-phenylalanine derivatives and their ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN SION NUMBER: 1987:85057 HCAPLUS Correction of: 1987:19047 106:85057 English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE (S): LS ANSWER 13 OF ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR (S): LANGUAGE SOURCE: TITLE:

| :   | KIND  | Ω. | DATE     | AP | APPLICATION NO. | DATE - 19860326 |
|-----|-------|----|----------|----|-----------------|-----------------|
|     | 3 S S |    | 19880224 | 7  | 1386-30211      | 0001            |
| G   | i m   | Н  |          |    |                 |                 |
| щ   |       |    | 19880308 | J. | JP 1986-61833   | 19860319        |
| A,  |       |    | 19890328 | ns | 1988-146719     | 1988            |
| [7] |       |    | 19950314 | ns | 1993-157564     | 19931123        |
|     |       |    |          | JP | 1985-62276      |                 |
|     |       |    |          | JP | 1986-38111      | A1 1986         |
|     |       |    |          | SD | 1986-844970     |                 |
|     |       |    |          | ns | 1988-146719     | _               |
|     |       |    |          | ns | 1989-844970     | B3 19890327     |

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10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

D-Phenylalanine derivs. D-RZCORN3CH(COZR1)CH2Ph [I] RI = H, C1-5 alkyl, C6-12 aryl or aralkyl, Q, CH2COZR3, CHMeCCOR3, CH2COCM43; R2 = (un)substituted C6-12 aryl, 5- or 6-membered heterocyclyl, cycloalkyl, cycloalkenyl; R3 = H, C1-5 alkyl], their salts. and precursors which can be converted thereto in the human or animal body, useful as hypoqlycemics, were prepared via conventional N-acylating reactions. D-Phenylalanine in 10% aqueous NaOH was successively treated with Me2CO, 4-ErCGH4COC1 in Me2CO, and 10% aqueous NaOH to give 83% acylphenylanine D-II. At 25 mg/kg in mice, D-II decreased blood glucose 34% in min. CASREACT 106:85057; MARPAT 106:85057 OTHER SOURCE(S):

use as hypoglycemic agents Toyoshima, Shigeshi; Seto, Yoshiko; Shinkai, Hisashi; Toi, Koji; Kumashiro, Izumi Preparation of D-phenylalanine derivatives and their 1111 APPLICATION NO. ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2007 ACS ON STN SION NUMBER: 1987:19047 HCAPLUS Ajinomoto Co., Inc., Japan Eur. Pat. Appl., 25 pp. CODEN: EPXXDW DATE 106:19047 English KIND PATENT ASSIGNEE(S): PATENT INFORMATION: L5 ANSWER 14 OF ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: PATENT NO. DOCUMENT TYPE: INVENTOR (S): SOURCE:

19860326 19850327

EP 1986-302217

19861001

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g,

R: CH, DE, FR, GI PRIORITY APPLN. INFO.: GI

EP 196222 A2

JP 1985-62276

-CONHCHCH2Ph

III

D-Phenylalanine derivs. D-R2CONR3CH(CO2R1)CH2Dh [I, R1 = H, C1-5 alkyl, C6-12 aryl or aralkyl, Q, CH2CO2R3, CHWGOCOR3, CH2COCOMG3; R2 = (un)substituted C6-12 aryl, 5- or 6-membered heterocyclyl, cycloalkyl, cycloalkryl, R3 = H, C1-5 alkyl], their salts, and precursors which can be converted thereto in the human or animal body, useful as hypoglycemics, were prepared via conventional N-acylating reactions. hypoglycemics, were prepared via conventional N-acylating reactions. D-Phenylalanine in 10% aqueous NaoM was successively treated with Me2CO, 4-ErC6H4COC1 in Me2CO, and 10% aqueous NaoM to give 83% acylphenylanine D-II. At 25 mg/kg in mice, D-II decreased blood glucose 34% in 60 min. ΑB

=> e US20050234129/prn,pn,an 4 US2005023311/PN E2 1 US2005023386/PN E3 0 --> US20050234129/PRN

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=> e US200500234129/prn,pn,an
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E3 0 --> US200500234129/PN
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=> d his

(FILE 'HOME' ENTERED AT 17:49:04 ON 02 MAY 2007)

'REGISTRY' ENTERED AT 17:49:18 ON 02 MAY 2007 STRUCTURE UPLOADED 5 IL SSS SAM 82 S. L1 SSS FULL 'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007 14 S L3/P 14 S SALT? AND L4 E US20050234129/PRN, PN, AN E US200500234129/PRN, PN, AN FILE FILE 222 15

=> s salt? (n2) nateglinide MISSING OPERATOR 'SALT? (N2' The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s salt? (w) nateglinide 1211784 SALT? 498 NATEGLINDE 16 0 SALT? (W) NATEGLINIDE

=> s" nateglinide salt?"
S" IS NOT A RECGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

498 "NATEGLINIDE" 801157 "SALT" 620279 "SALTS" "nateglinide salt?" s ^∥

searched 5/2/07 Page 19

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

("SALT" OR "SALTS")

1 "NATEGLINIDE SALT?"
("NATEGLINIDE"(W) "SALT") 1193024 "SALT"

IJ

d ibib abs

Sutton, Paul Allen; Vivilecchia, Richard Victor;
Parker, David John; De La Cruz, Marilyn
Novartis Ag, Switz.; Novartis Pharma Gmbh
PCT Int. Appl., 46 pp. Preparation and properties of nateglinide LT ANSWER 1 OF 1 HCAPIUS COPYRIGHT 2007 ACS on STN ACESSION NUMBER: 2003:737716 HCAPIUS DOCUMENT NUMBER: 139:230996 English LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE (S) DOCUMENT NUMBER: TITLE: DOCUMENT TYPE: INVENTOR (S): SOURCE:

20030310 20030310 20030310 20030310 20030310 20030310 20030310 20030310 20030310 20030310 20030310 20030310 20030310 CN, GH, CO, SC, SC, SE, 20030310 CA, CH, GD, GE, CH, ILK, LT, 1 RO, RU, ZA, CY, CZ, LY, RO, RU, ZA, CY, CZ, LY, RO, S E, 8 BZ, GB, LC, LC, VN, VN, CH, 3, GR, IT, LI, LU, N RA, TR, BG, CZ, E RR 2003-8316 JP 2003-574615 CN 2003-805803 US 2004-507255 US 2002-363178P WO 2003-EF2447 BR, BY, ES, FI, KR, KZ, PH, PL, UZ, VC, BE, BG, LU, MC, CA 2003-2478599 AU 2003-214112 EP 2003-709769 APPLICATION NO. WO 2003-EP2447 BG, KP, OM, US, IT, BB, KG, NZ, UA, TM, . 3 20030918 20030922 20041208 ES, FR, RO, MK, 20041228 20050707 20050720 AZ, DM, JP, NI, 20030918 AT, AU, DE, DK, IN, IS, MN, MX, TM, TM, TM, KZ, MD, FR, GB, FI, AA, CCZ, CZ, MK, TTJ, KG, KG, FI, A1 DE, LV, A A A1 ; 당 : BR 2003008316
JP 2005119949
CN 1642904
US 2002234129
PRIORITY APPLN. INFO.: R: AT, BE, TE, SI, 1 2003008316 2 2005519949 1 1642904 5 2005234129 1 2003214112 2478599 PATENT NO. E S E

The invention relates to salts of nateginide having specified properties (m.ps., solubilities, X-ray diffraction patterns) for use in pharmaceutical compns for preventing or treating diabetes, cardiovascular diseases, etc. Nateglinide Na. K, Cd. Mg, N-methyl-D-glucamine, TRIS, lysine, and ammonium salts were prepared and their properties tabulated. RENCE COUNT:

3 THERE ARE 3 CITED REFERENCES ANDLIABLE FOR THIS RENCE COUNT: REFERENCE COUNT: AB

> e US2005234129/Prn,pn,an 1 US2005234127/PN 1 US2005234128/PN 33 0 --> US2005234129/PN 4 1 US2005234129/PN 55 0 US2005234129/AN E3 E3 E3 E3

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CA, CH, CN,
GD, GE, GH,
LK, LT, LU,
YU, ZA, ZW,
YY, ZA, ZW
CY, CZ, DE,
PT, RO, SE,
ACCESSION NUMBER: 2003:737716 HCAPLUS
DOCUMENT NUMBER: 139:230996
TITLE: Reparation and properties of nateglinide salts
INVENTOR(S): Sutton, Paul Allen; Vivilecchia, Richard Victor; Parker, David John; De La Cruz, Marilyn Novartis Ag, Switz.; Novartis Pharma Gmbh SOURCE: CODEN: PIXXD2
                                                                                                                                                                   BZ,
LC,
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LANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
                                                                                                                                                                 W: AE, AG, P
CO, CR, C
LV, MA, N
SE, SG,
SW: AM, AZ, BW: DK, EE, E
                                                                                                                                                         WO 2003076393
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Page 21 searched 5/2/07

20030918 CA 2003-2478599 20030310 20030922 AU 2003-214112 20030310 EP 2003-709769 20030310 ES, FR, CB, GR, II, LI, LI, LI, SE, MC, PT,

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10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          (premenstrual syndrome; preparation and properties of nateglinide
                                                                                                                                                                                                                                       Kidney, disease (diabetic nephropathy; preparation and properties of nateglinide
                                                                                                                                                                                                                                                                                                                                                   Eye, disease (diabetic retinopathy; preparation and properties of nateglinide salts)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           Eye, disease (macula, degeneration; preparation and properties of nateglinide
                                                                                                                                                                                                                                                                                              Nerve, disease (diabetic neuropathy; preparation and properties of nateglinide
                                                                                                                                                                                                                                                                                                                                                                                                                       (foot; preparation and properties of nateglinide salts)
Kidney, disease
(glomerulosclerosis; preparation and properties of nateglinide salts)
   EE, HU,
                                                                                                                                                  (angina pectoris; preparation and properties of nateglinide
                                                                                                                                                                                     Artery, disease (coronary; preparation and properties of nateglinide salts
CY, AL, TR, BG, CZ, El

8 BR 2003-8316

DR 2003-574615

0 CN 2003-805803

0 US 2004-507255

US 2002-363178P

WO 2003-EP2447
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(infarction; preparation and properties of nateglinide
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              (impotence; preparation and properties of nateglinide
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IE, SI, LT, LV, FI, RO, MK,
BR 200308316 A 20041228
JP 2005519949 T 200550707
CN 1642904 A 200550720
US 2005234129 A1 20051020
PRIORITY APPLN. INFO::
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Cardiovascular system, disease
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       Cataract
Connective tissue, disease
Diabetes insipidus
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Antidiabetic agents
Antihypertensives
Antiobesity agents
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Osteoporosis
Skin, disease
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Hypertension
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Acidosis
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searched 5/2/07

Page 22

(preparation and properties of nateglinide salts)
Hyperlipidemna
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation and properties of nateglinide salts) II II

Artery, disease (restenosis; preparation and properties of nateglinide salts)

Brain, disease H

(stroke; preparation and properties of nateglinide salts

Inflammation Ħ

Intestine, disease (ulcerative colitis; preparation and properties of nateglinide

50-99-7, D-Glucose, biological studies RL: BSU (Biological study, unclassified); BIOL (Biological study) (impaired tolerance; preparation and properties of nateglinide H

594837-86-2P RI. PRP (Properties), RCT (Reactant); RACT (Reactant or reagent)
(preparation and properties of nateglinide salts)
(preparation and properties of nateglinide salts)
59252-32-32-95
59253-31-4P
59253-31-4P
594837-88-4P
594837-89-5P
RI. PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and properties of nateglinide salts)
9004-10-8, Insulin, biological studies
RI. BSU (Biological study, unclassified); BIOL (Biological study)
(resistance; preparation and properties of nateglinide 105816-04-4, Nateglinide H H

H

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT REFERENCE COUNT:

TOTAL SESSION -11.70 TOTAL SESSION 260.93 SINCE FILE ENTRY -11.70 ENTRY 88.17 SINCE FILE DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) => fil stng
COST IN U.S. DOLLARS CA SUBSCRIBER PRICE FULL ESTIMATED COST

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=> s 105816-04-4/rn or 592523-31-4/rn or 592523-32-5/rn or 592524-24-8/rn or 594837-85-1/rn or 594837-86-2/rn or 594837-87-3/rn or 594837-88-4/rn or 594837-89-5/rn or 189-5/rn or 189-5/rn or 189-5/rn or 180-5/rn or 180-5/r

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searched 5/2/07 Page 23

-str\_regno\_text -Search 10/507255 SALTS OF NATEGLINIDE

18

0 594837-85-1/RN 0 594837-86-2/RN 0 594837-88-4/RN 0 594837-88-4/RN 0 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524-24-8/RN OR 594837-85-1/RN OR 594837-86-2/RN OR 594837-87-3/RN OR 594837-88-4/RN OR 594837-88-5/RN

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HIGHEST RN 934050-43-8 HIGHEST RN 934050-43-8 1 MAY 2007 1 MAY 2007 STRUCTURE FILE UPDATES: DICTIONARY FILE UPDATES: New CAS Information Use Policies, enter HELP USAGETERMS for details.

ISCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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13

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The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are:  $(RN = CAS\ Registry\ Number)$ 

- Index Name, MF, and structure - no RN
- All substance data, except sequence data
- FIDE, but only 50 names
- IDE, plus sequence data
- Same as SQIDE, but 3-letter amino acid codes are used
- Protein sequence data, includes RN
- Same as SQD, but 3-letter amino acid codes are used
- Protein sequence name information, includes RN

REG SAM FIDE IDE SQIDE SQIDE3 SQD SQD3

- Table of calculated properties - Table of experimental properties - EPROP and CALC CALC EPROP PROP

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

-- Abstract

-- Application and Priority Information, -- CA Accession Number, plus Bibliographic Data -- CA Accession Number, plus Bibliographic Data (compressed) ABS --APPS --BIB --CAN --CBIB --IND --IPC --PATS --STD ---

-- International Patent Classification

-- Index Data

-- BIB, IPC, and NCL

-- ABS, indented, with text labels -- BIB, indented, with text labels IABS -- ABS, indented, with to IBIB -- BIB, indented, with to ISTD -- STD format, indented

OBIB ------ AN, plus Bibliographic Data (original) OIBIB ----- OBIB, indented with text labels

SBIB ----- BIB, no citations SIBIB ----- IBIB, no citations

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The MAX format is the same as ALL. The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

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HELP DFIELDS -- To see a complete list of individual display fields. HELP FORMATS -- To see detailed descriptions of the predefined formats. ENTER DISPLAY FORMAT (IDE):ide

searched 5/2/07 Page 25

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

594837-89-5 REGISTRY
Entered STN: 29 Sep 2003
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
STEREOSEARCH
STEREOSEARCH
STEREOSEARCH 3 2 B 3

C19 H27 N O3 . x H3 N

CA, CAPLUS, USPATFULL (105816-04-4) STN Files: FS MF SR CRN

Absolute stereochemistry.

NH3

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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(FILE 'HOME' ENTERED AT 17:49:04 ON 02 MAY 2007)

'REGISTRY' ENTERED AT 17:49:18 ON 02 MAY 2007 STRUCTURE UPLOADED 5 L1 SSS SAM 82 S L1 SSS FULL FILE

SEE

'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007 FILE

4 4 S 13/P 14 S SALT? AND L4 E US20050234129/PRN, PN, AN E US200500234129/PRN, PN, AN E NATEGLINIDE+ALL/CT 0 S SALT? (W) NATEGLINIDE 1 S "NATEGLINIDE SALT?" E US2005234129/PRN, PN, AN

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FILE 'STNGUIDE' ENTERED AT 18:00:24 ON 02 MAY 2007 0 S 105816-04-4/RN OR 592523-31-4/RN OR 592523

FILE 'REGISTRY' ENTERED AT 18:04:27 ON 02 MAY 2007 9 S 105816-04-4/RN OR 592523-31-4/RN OR 592524

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ANSWER 1 OF 9 REGISTRY COPYRIGHT 2007 ACS on STN CERE

594837-89-5 REGISTRY
Entered STW: 29 Sep 2003
Entered STW: 29 Sep 2003
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
ammonium salt (9CI) (CA INDEX NAME)
STEREOSEARCH
C19 H27 N O3 . x H3 N

FS MF SR LC CRN

CA, CAPLUS, USPATFULL STN Files: (105816-04-4)

Absolute stereochemistry.

• x NH3

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1907 TO DATE)
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Magnesium, bis IN-[[Lanch 1007 ACS on STN Magnesium, bis IN-[[Lanch 100] (CA INDEX NAME)] CCS H52 Magnesium, bis IN-[[Lanch 100] (CA INDEX NAME)] CCS H52 Mg N2 06 CCS CCS H52 Mg N2 06 CCS STN Files: CA, Capt... CN EBN CN

searched 5/2/07 Page 27

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ANSWER 3 OF 9 REGISTRY COPYRIGHT 2007 ACS on STN 594837-87-3 REGISTRY

Entered STN: 29 Sep 2003
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, calcium salt (2:1) (9C1) (CA INDEX NAME)
STBREGGEARCH
C19 H27 N 03 . 1/2 Ca

STN Files: CA, CAPLUS, USPATFULL (105816-04-4) FS SR CRN

Absolute stereochemistry.

S 01/2 \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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ANSWER 4 OF 9 REGISTRY COPYRIGHT 2007 ACS on STN 594837-86-2 REGISTRY Entered STN: 29 Sep 2003 Entered STN: 29 Sep 2003 Entered STN: (29 Sep 2003 Entered STN: 29 Sep 2003 Entered STN: (20 Sep 2003 Entered Statum salt (9CI) (CA INDEX NAME) STEREOSEARCH

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Absolute stereochemistry.

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ANSWER 5 OF 9 REGISTRY COPPRIGHT 2007 ACS on STN
549817-85-1 REGISTRY
Entered STN: 29 2003
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
morosodaum salt [9CI] (CA INDEX NAME)
STRENGOSEARCH
C19 H27 N 03 . Na S E B S

STN Files: CA, CAPLUS, USPATFULL (105816-04-4) FS SR CRN CRN

Absolute stereochemistry.

• Na

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1907 TO DATE) 2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L9 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2007 ACS on STN

searched 5/2/07 Page 29

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

ES ES CERT

592524-24-8 REGISTRY
Entered STN: 25 Sep 2003
Entered STN: 25 Sep 2003
Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with L-lysine (1:1) (9CI) (CA INDEX NAME)
STEREOSEARCH

C19 H27 N O3 . C6 H14 N2 O2

CA, CAPLUS, USPATFULL CA STN Files:

G G

CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

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CRN 56-87-1 CMF C6 H14 N2 O2

Absolute stereochemistry.

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ANSWER 7 OF 9 REGISTRY COPYRIGHT 2007 ACS on STN 592523-32-5 REGISTRY Entered STN: 25 86P 2003 D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (9CI) (CA INDEX SEES

STEREOSEARCH C19 H27 N 03 . C4 H11 N 03

CA, CAPLUS, USPATFULL CA STN Files: SF A S 그

CRN 105816-04-4

CMF C19 H27 N 03

Absolute stereochemistry.

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CRN 77-86-1 . CMF C4 H11 N O3

но-сн2-с-сн2-он CH2-OH \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

Lucred STN: 25 Sep 2003
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. STREREOSEARCH
C19 H27 N O3 . C7 H17 N O5
CA H27 IN O5
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CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

searched 5/2/07 Page 31

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

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CRN 6284-40-8 CMF C7 H17 N O5

Absolute stereochemistry.

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE) 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L9 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2007 ACS on STN
N 105816-604-4 REGISTRY
ED Entered STN: 21 Dec. 1986
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (
NDER CA INDEX NAME):
OTHER CA INDEX NAMES:
CN D-Phenylalanine, N-[[4-(1-methylethyl)cyclohexyl]carbonyl]-, trans-

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[-]-N-[(trans-4-Isopropylcyclohexyl)carbonyl]-D-phenylalanine

A 4166 AY 4166

D-Nateglinide DJN 608

Nateglinide SDZ-DJN 608

Senaglinide

starlix

Starlix DS

ONTHER NAMES:
CN 74-16-6
CN 74-416-6
CN 74 Starsis

STEREOSEARCH 418766-62-8 C19 H27 N O3

STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, ENBASE, IMSDRUGNEWS, INSPATENTS, INSRESEARCH, IPA, MEDLINE, PMCK\*, PATUPASPEC, PHAR, PIRA, PROWT, PROUSDDR, PS, RTECS\*, SCISEARCH, SYNTHINE, TOXCENTER, USARN, USPATZ, USPATFULL (\*File contains numerically searchable property data)

Absolute stereochemistry.

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

535 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

| 538 REFERENCES IN FILE CAPLUS (1907 TO DATE) | 1S (1907 TO DATE) |        |
|--|-------------------|--------|
| => fil stng<br>COST IN U.S. DOLLARS          | į                 | TOTAL  |
| FULL ESTIMATED COST                          | 21.30 282.65      | 282.65 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)   | SINCE FILE        | TOTAL  |
| CA SUBSCRIBER PRICE                          | 0.00 -1           | -11.70 |

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searched 5/2/07 Page 33

FILE 'REGISTRY' ENTERED AT 18:04:27 ON 02 MAY 2007 9 S 105816-04-4/RN OR 592523-31-4/RN OR 592524 IGUIDE' ENTERED AT 18:00:24 ON 02 MAY 2007 0 S 105816-04-4/RN OR 592523-31-4/RN OR 592523-32-5/RN OR 592524 New CAS Information Use Policies, enter HELP USAGETERMS for details. This file contains CAS Registry Numbers for easy and accurate substance identification. FILE 'REGISTRY' ENTERED AT 17:49:18 ON 02 MAY 2007 FILE 'HCAPLUS' ENTERED AT 17:50:19 ON 02 MAY 2007 (FILE 'HOME' ENTERED AT 17:49:04 ON 02 MAY 2007) VOL 146 ISS 19 (20070501/ED) 44 S L3/P
14 S SALT? AND L4
E USZO050234129/PRN, PN, AN E USZO0500234129/PRN, PN, AN E USZO050024129/PRN, PN, AN E SALT? (W) NAREGLINDE
1 S "RATEGLINIDE SALT?"
E USZO05234129/PRN, PN, AN STRUCTURE UPLOADED 5 S L1 SSS SAM 82 S L1 SSS FULL FILE COVERS 1907 - 2 May 2007 FILE LAST UPDATED: 1 May 2007 FILE 'STNGUIDE' => d his 17 87 13 SEE 15

FILE 'STNGUIDE' ENTERED AT 18:06:38 ON 02 MAY 2007 FILE 'HCAPLUS' ENTERED AT 18:07:36 ON 02 MAY 2007

=> d 14 1-44 ibib abs

20060721 Preparation of H type nateglinide crystal Chen, Songnian: Feng, Qianjian; Yu, Yingmin Hangzhou Pollen Co., Ltd., Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, 5pp. CODEN: CNXXEV DATE CN 2006-10052617 CN 2006-10052617 APPLICATION NO. L4 ANSWER 1 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2007:14393 HCAPLUS DOCUMENT NUMBER: 146:163387 20070103 DATE Chinese KIND COUNT: PATENT ASSIGNEE(S): FAMILY ACC. NUM. CC PATENT INFORMATION: PATENT NO. DOCUMENT TYPE: INVENTOR(S): LANGUAGE: SOURCE:

PRIORITY APPLN. INFO.: CASREACT 146:163387

OTHER SOURCE(S):
AB The title method comprises the steps of: (1) condensing trans-4-isopropylcyclohexanecarbonyl chloride with D-phenylalanine to

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CN 1887858

obtain crude crystal of B type nateglinide, (2) dissolving the crude crystal in the solution of methanol, aminomethane and water (volume ratio of 60:20:20), heating to 40-60°C, adding 2% active carbon, decoloring for 7-15 min, filtrating, cooling to 10°C to precipitate, filtrating, washing with 40% ethanol till neutral, and dfying to obtain H type nateglinide crystal, and (3) recrystg, the mother solution to obtain H type nateglinide crystal. The product of H type nateglinide crystal has good physiol. activity.

Process for the preparation of nateglinide, preferably in B-form Vigano, Enrico: Pizzatti, Enrica: Lanfranconi, Simona; Molteni, Renato: Landonio, Ernesto ANSWER 2 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN Italy U.S. Pat. Appl. Publ., 22 pp. CODEN: USXXCO 2006:657506 HCAPLUS 145:103952 Patent English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE(S): L4 ANSWER 2 OF 4 ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR (S): LANGUAGE: SOURCE:

The invention relates to a process for the preparation of nateglinide, preferably in B-form, substantially free from the H-form, comprising three steps starting from (i) reaction in an organic solvent between D-phenylalanine Me ester or a salt and trans-4isopropylcyclohexancarboxylic acid in the presence of an acyl chloride or carbonyldimidazole, optionally isolating the nateglinide Me ester or betained and re-dissolving it in a second organic solvent, (ii) addition of water and alkali hydroxide to the reaction mixture and separation of the 20050103 APPLICATION NO. US 2005-28283 US 2005-28283 CASREACT 145:103952 20060706 DATE KIND A1 PRIORITY APPLN. INFO.: OTHER SOURCE(S): US 2006148902 PATENT NO.

phase containing the alkali salt of nateglinide, and (iii) addition of hydrochloric acid to the aqueous phase from step (ii) to obtain nateglinide. In an example, the reaction was carried out in acetone in the presence of triethylamine and Et chloroformate and hydrolysis of nateglinide Me ester was carried out using toluene, tricaprylmethylammonium chloride, and aqueous potassium hydroxide to afford nateglinide in B-form (130.44°C). aqueous

Direct separation and enantioseparation of nateglinide stereoisomers by HPLC strain, Yanjie; Zhang, Qiming; Li, Huiyi; Ning, Baoming; Liu, Wanying; Tian, Songjiu China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China Peop. Rep. China Saxhi (2005), 25(6), 657-659 CODEN: YEZADL; ISSN: 0254-1793 L4 ANSWER 3 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2006:328161 HCAPLUS DOCUMENT NUMBER: 145:173833 CORPORATE SOURCE: AUTHOR (S): SOURCE:

searched 5/2/07 Page 35

DOCUMENT TYPE: LANGUAGE:

PUBLISHER:

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

An HPLC method was developed to sep. the enantiomers of nateglinide as well as trans-nateglinide and cis-nateglinide. The nateglinide enantiomers, trans-nateglinide and cis-nateglinide were directly separated on a HPLC chiral stationary phase consisting of the Kromasil TBB with hexane-2-propanol-acetic acid (95:5:0.2) as eluent and a flow rate of 0.6 mL·min-1 at 258 nm and 20°C. Three kinds of Nateglinide could be completely separated, and the resolns were 2.38 and 1.85, resp. The method can be used for separating the nateglinide enantiomers, trans-nateglinide and cis-nateglinide and determining content of nateglinide.

One-pot process for the preparation of nateglinide Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra; Singh, Manjinder; Birari, Dilip Ramdas Cipla Limited, India; Wain, Christopher Paul CODEN: PIXXD2 COPYRIGHT 2007 ACS on STN 2005:1328488 HCAPLUS 144:51894 English Patent HCAPLUS FAMILY ACC. NUM. COUNT: PATENT INFORMATION: ANSWER 4 OF 44 L4 ANSWER 4 OF 4 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE(S) DOCUMENT TYPE: INVENTOR(S): SOURCE:

EV. EM. ZM., ZM., ZM. GH., GM., MZ, NA, SD, SL, SZ, TZ, UG, ZM., ZW., AM., AZ, BY. KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, CG, GR, HU, IE, IT, LU, MC, NL, PT, FO, ES, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GM, ML, MR, NE, SN, TD, TG

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Al 2005122

AU 2005252002

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AL 2005-252002

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AL 2005-252002

Al 20050608

CA 2570041

Al 20070328

EP 2005-750279

CA 2670041

Al 20070328

EP 2005-750279

CA 2670041

Al 20070328

CA 2670041

Al 20070328

CA 2670041

Al 20070328

CA 2670041

A 20040611

GB 2004-13084

A 20040611

OTHER SOURCE(S):

CASREACT 144:51894, MARPAT 144:51894

A 000-pct process for the preparation of nategilinide is presented which comprises amidation of a Cl-4 alkyl ester of D-phenylalanine, either as the free base or in salt form (typically the Mydrochloride), with trans-4-isopropyleyclohexanecarboxylic acid or its acid halides to obtain a Cl-4 alkyl ester of nategilinide, preferably the Me ester of nategilinide in preparation and acidification (e.g., MG) appearance connecessory in the preparation of nategilinide in preparation (e.g., MC) and preparation a Cl-4 alkyl ester of nategilinide in preparation and acidification (e.g., MC) and preparation and acidification (e.g., MC) and preparation and connecessory in the preparation and connecessory in the preparation and acidification (e.g., MC) and antegilinide (m.p. 128-131). 20050608 BZ, CA, CH, FI, GB, GD, KP, KR, KZ, MX, MZ, NA, SE, SG, SK, VC, VN, YU, ES, KM, SD, UZ, KG, KG, SC, US, APPLICATION NO. WO 2005-GB2267 BG, FG, WG, BB, DZ, IS, MD, TZ, 20051222 AU, AZ, DE, DK, ID, IL, LU, LV, I PG, PH, I THE CZ, KIND A1 CU, HR, LS, TJ, R: AT, BE, BG, IS, IT, LI, PRIORITY APPLN. INFO:: WO 2005121071 PATENT NO.

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT OTHER SOURCE(S): REFERENCE COUNT

L4 ANSWER 5 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2005:1261034 HCAPLUS

Venkataraman, Sundaram; Narsapur, Sharat Pandurang; Venkatar, Manoj Ramesh; Banqarubabu, Rongalli, Sandeep, Mohanty, Sayantani, Pyne; Raju, Kakarlapudi Ranga Dr. Reddy's Laboratories Ltd., India; Dr. Reddy's Laboratories, Inc. PCT Int. Appl., 14 pp. Stable nateglinide form b compositions via crystallization Patent English LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT ASSIGNEE (S): DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): SOURCE:

PATENT INFORMATION

20040520 20040708 20050118 **表界に再** 20050520 A B K K S K K ZW, DE, GW, SZ, SZ, SZ, BY, ES, KM, NW, UZ, SKY, G BR, BW, EE, EG, KE, KG, MK, MN, RU, SC, UG, US, US 2004-572689P US 2004-586431P US 2005-644614P WO 2005-US17664 APPLICATION NO. SZ, ET, CM, BG, EC, SI, II, BB, DZ, IS, MD, PT, TZ, SD, IS, BA, IN, MA, TT, AU, AZ, DE, DK, ID, IL, LU, LV, PG, PH, TN, TR, MZ, TJ, HU, BJ, 20051201 RU, GR, AT, HU, LIT, TM, នុំ**ម៉ូ**ម៉ូង៉ូង KIND
A2
AM, A
CU, C
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LS, L
LS, C
NZ, C
TJ, T A X E X 5 PRIORITY APPLN. INFO.: WO 2005113485 PATENT NO. RM:

ij

A process for preparing nateglinide Form B comprises dissolving nateglinide (I) in a solvent and adding the solution, at temps. of  $40+45^\circ$ C, to a hydrocarbon liquid that is at temps. of  $40+5^\circ$ C. Then, water is added and the mixture is allowed to cool, producing crystals of nateglinide B

ANSWER 6 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN 2SION NUMBER: 2005:1240947 HCAPLUS 4ENT NUMBER: 144:11582 14 ANSWER 6 OF 44
ACCESSION NUMBER:
DOCUMENT NUMBER:
TITLE:

Form B.

Process for the preparation of polymorphic crystalline forms of natedlinide ammonium salt Wizel. Shomit: Frenkel, Gustavo; Gome, Boaz Teva Pharmaceutical Industries Ltd., Israel; Teva INVENTOR(S): PATENT ASSIGNEE(S):

searched 5/2/07 Page 37

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

Pharmaceuticals Usa, Inc. PCT Int. Appl., 25 pp. CODEN: PIXXD2 Patent FAMILY ACC. NUM. CC PATENT INFORMATION: DOCUMENT TYPE: LANGUAGE

CN 1950331 A 20070418 CN 2005-80014509 20050509
PRIORITY APPLN. INFO.: WO 2005-US16343 W 2005050
AB Anti-hyperglycemic polymorphic crystalline forms of nateglinide ammonium salt 20050509 CA, CH, GB, GD, KR, KZ, MZ, NA, SG, SK, ZM, ZW, AM, CZ, DE, DK, NL, PL, PT, GQ, GW, ML, 20050509 20050509 20050509 SE, MC, PT, HU, PL, SK, S, C, C, S, S, S, C, S, ES, FR, GB, GR, II, LI, LU, NL, RO, MK, CY, AL, TR, BG, CZ, EE, BY, ES, KM, SD, MO 2005-US16343 BB, BG, BR, BW, DZ, EC, EE, EG, IS, DR, KE, KG, MD, MG, MK, MM, PT, RO, RU, SC, TZ, UA, UG, US, CA 2005-2563793 US 2005-126050 EP 2005-748381 5 E E E APPLICATION NO. SZ, BG, LT, CM, SD, AT, IS, CG, 20051124 AU, AZ, DE, DK, ID, IL, LU, LV, PG, PH, 20051124 20060105 20060517 MZ, TJ, HU, BJ, MW, RU, GR, E, E 3,6,8,5,5 A CH, CA, MO 2005110972

WO 2005110972

W. AE, AG, A.

CN, CO, CR

GE, IK, IR,

IC, IK,

I , BE, CH, , SI, LT, , HR, IS, CA 2563793 US 2006004102 EP 1656339 are prepared REFERENCE COUNT:

THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 12

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ANSWER 7 OF 44

Synthesis of nateglinide analogs and their bioactivity Zhang, Jianxin; Dong, Junjun; Han, Han; Gong, Zehui; Huang, Shijie; Liu, Keliang Institute of Pharmacology and Toxicology, Academy of Military Medical Sciences, Beijing, 100850, Peop. Rep 2005:841495 HCAPLUS 145:315230 determination ACCESSION NUMBER: CORPORATE SOURCE: DOCUMENT NUMBER: AUTHOR(S):

Zhongguo Yaowu Huaxue Zazhi (2004), 14(6), 335-339, CODEN: ZYHZEF; ISSN: 1005-0108 China SOURCE:

Analogs of nateglinide [i.e., N-[[trans-4-(1-methylethyl)cyclohexyl]carbon yl]-D-phenylalanine] were synthesized, and their biol. activities were tested by glycemia levels in mice. The new compads. were synthesized using N-[isopropyl]pherazine, N.isopropyl-4-piperidinecarboxylic acid, trans-4-dimethylamino-1-cyclohexanecarboxylic acid and substituted Zhongguo Yaowu Huaxue Zazhi Bianjibu Journal Chinese CASREACT 145:315230 LANGUAGE: OTHER SOURCE(S): PUBLISHER: DOCUMENT TYPE: æ

phenylalanine as the starting materials. The biol. activities of the new compds. were tested by the glycemia levels in mice via drug administration after forbiddance of food-intake and oral delivery of glucose. Forty-three new compds. were synthesized, and their structures were confirmed by elementary anal., IR, polarimetric anal., IH-NMR and MS. One pompound, 4-fluoro-N-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-I-phenylalanine monohydrochloride, showed significant hypoglycemic effect on qlycemia of mice, and had an (S)-configuration at the chiral center, which was opposite to the control.

Improved process for the preparation of hypoglycemic agent nateglinide Schong, Bohus; Wu, Bo; Yan, Yuan Toxic Drug Har, Academy of Military Medical Science, PLA, Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. ANSWER 8 OF 44 HCAPLUS COPYRIGHT 2007 ACS ON STN SION NUMBER: 2005:476519 HCAPLUS CODEN: CNXXEV 143:97635 Chinese Patent LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT ASSIGNEE(S): PATENT INFORMATION: L4 ANSWER 8 OF ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): SOURCE: TITLE:

PRIORITY APPIN. INFO.: CASREACT 143:99635

AB A scalable process for the preparation of nateglinide, a hypoglycemic agent, was reported. The key improvement is that the acylation of D-phenylalanine with 4-isopropylcyclohexanecarbonyl chloride was performed under a homogeneous condition using a mixture of dioxane or THF and H2O as solvent, largely increasing the yield. Other features include the use of cheap Pd/C instead of previously expensive PtO2 as hydrogenation catalyst in the reduction of 4-isopropylboric acid into 4-isopropylcyclohexanecarboxylic acid. Purification of nateglinide by recrystn. In petroleum ether, hexane and cyclohexane or their mixts. is claimed. 20030117 APPLICATION NO. CN 2003-100559 CN 2003-100559 20040804 KIND 4 CN 1517335 PATENT NO.

Improved process for the preparation of hypoglycemic agent nateglinide Thu, Qir, Pan, Uniferng Shi, Mingfeng Shanhai Huashuo Medicine Science & Technology Development Co., Ltd., Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. L4 ANSWER 9 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACESSION NUMBER: 2005:476518 HCAPLUS DOCUMENT NUMBER: 143:26875 CODEN: CNXXEV Chinese given COUNT: INVENTOR(S): PATENT ASSIGNEE(S): PATENT INFORMATION: FAMILY ACC. NUM. DOCUMENT TYPE: LANGUAGE SOURCE:

searched 5/2/07 Page 39

APPLICATION NO.

DATE

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PATENT NO.

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

A scalable process for the preparation of nateglinide, a hypoglycemic agent, was reported. The key improvement is that the acquation of Drphenylalanine with 4-isopropylcyclohexanecarbonyl chloride was performed under a homogeneous condition using a mixture of DMF and H2O as solvent, largely increasing the yield. Other features include the use of cheap Pd/C instead of previously exposible Pto2 as hydrogenation catalyst in the reduction of 4-isopropyleoractic acid into 4-isopropylcyclohexanecarboxylic CN 2003-114970 CN 2003-114970 CASREACT 143:26875 20040804 Ą PRIORITY APPLN. INFO.: OTHER SOURCE(S): CN 1517334

Process for the preparation of the crystalline B-form nateglinide from D-phenylalanine methyl ester and trans-4-isopropylcyclohexanecarboxylic acid Vigano', Enrico; Pizzati, Enrica; Lanfranconi, Simona; Molteni, Renato; Landonio, Ernesto A.M.S.A. Anonima Materie Sintetiche e Affini S.p.A., HCAPLUS COPYRIGHT 2007 ACS on STN 2005:467801 HCAPLUS Eur. Pat. Appl., 32 pp. CODEN: EPXXDW 143:7982 English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L4 ANSWER 10 OF 44 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE(S): DOCUMENT TYPE: INVENTOR (S): LANGUAGE: SOURCE:

NL, SE, MC, PT, EE, HU, SK 20031126 A 20031126 20031126 DE, DK, ES, FR, GB, GR, IT, LI, LU, LV, IV, FI, RO, MK, CY, AL, FR, BG, CZ, T 20070115 AT 2003-27114 EP 2003-27114 APPLICATION NO. EP 2003-27114 20050601 20061227 DATE KIND R: AT, BE, CH, IE, SI, LT, PRIORITY APPLN. INFO.: EP 1535900 EP 1535900 PATENT NO. AT 349418

OTHER SOURCE(S):

AB A process for the preparation of nateglinide comprises: (I) the amidation reaction in a first organic solvent between D-phenylalanine Me ester, or a salt, and trans-4-isopropylcyclohexanecarboxylic acid and an acyl chloride, or carbonylalanide Me ester; (Ia) optionally isolating the nateglinide Me ester; (Ia) optionally isolating the nateglinide Me ester and redissolving it in a second organic solvent to give a solution; (II) addition of water and alkali hydroxide to the reaction mixture coming from step (I) without isolating the nateglinide Me ester, or, if applicable, to the solution of step (Ia), and separation of the aqueous phase containing the alkali salt of nateglinide; (III) addition

of hydrochloric acid to the aqueous phase coming from step (II) to obtain nateginide , wherein the organic solvent employed in step (II) is a water non-miscible solvent 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RENCE COURT: THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT REFERENCE COUNT:

PLUS COPYRIGHT 2007 ACS on STN 2005:414565 HCAPLUS 142:482315 L4 ANSWER 11 OF 44 HCAPLUS ACCESSION NUMBER: 2005: DOCUMENT NUMBER:

Preparation of alanine derivative as antidiabetics Yang, Yushe; Tang, Lei; Ji, Ruyun; Chen, Kaixian INVENTOR(S):

Sciences, Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, 26 pp. CODEN: CNXXEV Shanghai Institute of Pharmacy, Chinese Academy of PATENT ASSIGNEE (S): SOURCE:

Patent

Chinese DOCUMENT TYPE:

LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

20030124 CASREACT 142:482315; MARPAT 142:482315 CN 2003-115160 CN 2003-115160 APPLICATION NO. 20030723 DATE KIND ď APPLN. INFO.: CN 1431197 PRIORITY APPLN. IN OTHER SOURCE(S): PATENT NO.

Alanine derivs. I (RI = 2-(1-indoly1)ethy1, 2-[N-(2-benzoxazoly1)-N-methy1) annoethy1, 2-[N-methy1-2-pyridiny1)]annoethy1, 2-[N-methy1-2-pheny1-4-oxazoly1)ethy1, 4-trifluoromethy1benzy1, benzy1; R2 = 1, alky1) is prepared by condensation reaction of trans-4-isopropy1cyclohexancezboxy1c acid N-succining141 ester with Loor D-tyrosine Me ester in inext solvent to obtain 3-(4-hydroxypheny1)-2-(trans-isopropy1cyclohexylcarboxamido)propanoic acid Me ester (II), Mitsunob reaction with aromatic al., and then hydrolysis with inorgy base solution The method may be prepared by (I) etherification of II with allow protected 2-methylaminoethanol, condensation reaction with 2-fluoropyridine, and hydrolysis of II; or (3) condensation reaction with 2-fluoropyridine, and hydrolysis with base. The alanine derivative and its all may be used to prepare the medical prepns. for treating type II æ

L4 ANSWER 12 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2005;249676 HCAPLUS DOCUMENT NUMBER: SURPhoson and Litte:

diabetes mellitus.

Syntheses and hypoglycemia activities of N-(trans-4-isopro-pylcyclohexylcarbonyl)-  $\beta\text{-ring}$ 

substituted phenylalanines
Pan, Man-gen; Liang, Yuan-jun; Li, Bi-hai; Zhong,
Bo-hua; Huang, Shi-jie; Gong, Ze-hui; Liu, Ke-liang
Institute of Pharmacology and Toxicology, Academy of
Military Medical Sciences, Beijing, 100850, Peop. Rep.

CORPORATE SOURCE:

AUTHOR (S):

Zhongguo Yaowu Huaxue Zazhi (2003), 13(5), 249-253

searched 5/2/07 Page 41

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

CODEN: ZYHZEF; ISSN: 1005-0108 Zhongguo Yaowu Huaxue Zazhi Bianjibu

Journal

DOCUMENT TYPE:

PUBLISHER:

CASREACT 144:88520 LANGUAGE: OTHER SOURCE(S):

condensation of substituted phenylalanine derivs. with trans-4-isopropylycyclohexanecarbonyl chloride. 3-Fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]-crabonyl-i-phenylalanine was prepared and showed hypoglycemic activity comparable to that of nateglinide. A series of title compds. were synthesized as nateglinide (N-(trans-4-isopropylcyclohexyl-1-carbonyl)-D-phenylalanine) analogs by

ANSWER 13 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN SION NUMBER: 2005:204069 HCAPLUS ENT NUMBER: 142:482313 L4 ANSWER 13 OF ACCESSION NUMBER: DOCUMENT NUMBER:

INVENTOR (S):

TITIE:

treatment of blood sugar disorders
Liu, Kellang, Pan, Mangen; Liang, Yuanjun; Zhong,
Bohua; Li, Bihai; Huang, Shijie; Li, Xin; Dong,
Huajin; Chi, Mugen
Institute of Toxicant and Pharmaceuticals, Academy of
Military Medical Science of PlA, Peop. Rep. China
Faning Zhuanli Shenqing Gongkai Shuomingshu, 41 pp. PATENT ASSIGNEE (S):

Patent Chinese DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

20030425 A 20020426 A 20031105 CN 2003-123272 CN 2002-116715 CASREACT 142:482313; MARPAT 142:482313 APPLICATION NO. DATE KIND PRIORITY APPLN. INFO.: OTHER SOURCE(S): GI CN 1453265 PATENT NO.

(--co-NH-CH-(CH2)n-Ar

The aromatic amino acid derivs. I (n = 0, 1; X, Y = C, N; Ar = benzene ring substituted by one or more substituents (such as halo, NO2, OH, CCOH, CF3, trifluoromethoxy, methylenedicthio, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkenyl, alkenoxy, alkenoxy, phenoxy, benzyloxy, ester group, amino, amido), other aromatic ring, heterocyclic ring or its substituted derivative, useful for the treatment of blood sugar disorders, were prepared by acylation of 3-arylalanine HCl with 4- isopropylcyclohexylcarbonyl chloride or l-isopropyl-4-piperidinylcarbonyl chloride. Thus, reaction of D-3-hitrophenylalanine hydrochloride with aqueous NaOH at room temperature for 5 h gave, after acidification with ΑB

71.1% N-(trans-4-isopropylcyclohexanecarbonyl)-D-3-nitrophenylalanine (II). II showed endothelin receptor antagonist activity at 10-9mol/L. aqueous HC]

| 1.4 ANSWER 14 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN CACCSSION UNMERS: 2005:59980 HCAPLUS DOCUMENT NUMBER: 142:1411289 | Crystalline form of nateglinide<br>Frenkel, Gustavo; Gome, Boaz; Wizel, Shlomit<br>Israel | U.S. Pat. Appl. Publ., 91 pp., Contin-part of U.S. Ser. No. 622,905. | Patent<br>English           | 4 ··   |
|---|---|--|-----------------------------|--|
| L4 ANSWER 14 OF 44 ACCESSION NUMBER: DOCUMENT NUMBER:   | TITLE:<br>INVENTOR(S):<br>PATENT ASSIGNEE(S):   | SOURCE:  | DOCUMENT TYPE:<br>LANGUAGE: | FAMILY ACC. NUM. COUNT:<br>PATENT INFORMATION: |

BZ, CA, CH, FI, GB, GD, KR, KZ, LC, MZ, NA, NI 20040113 SE, MC, PT, HU, SK 20040113 20031224 20021105 0030616 20030718 0040113 20030123 20031224 2002002 20021212 20030718 20031023 BY, ES, KP, MX, NL, EE, BA, BB, BG, BR, BW, E
DM, DZ, EC, EE, EG,
IN, IS, JP, KE, KG, KK
MD, MG, MK, MN, MW, M
EP 2004-701856
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CY, AL, TR, BG, CZ, E
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US 2002-432962P
US 2002-432962P
US 2002-432962P
US 2003-622395
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US 2003-623395 US 2003-746697 US 2003-622905 CA 2004-2513753 WO 2004-US839 APPLICATION NO. 20040916 20040812 20040812 AU, AZ, DE, DK, ID, IL, IV, MA, 20050309 ES, FR, RO, MK, 20060920 20050120 0041209 DATE EG, X, I KIND
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LOE, I ች **.** ይ ይ . 3 유다. PRIORITY APPLN. INFO.: R: AT, BE, IE, SI, US 2005014836 US 2004181089 CA 2513753 WO 2004067496 CN 1835912 US 2007004804 PATENT NO. EΡ

Crystalline forms of nateglinide and processes for their preparation, as well pharmaceutical formulations containing them and methods of administration are AB

steps of (a) preparing a solution of nateglinide in Et acetate, (b) seeding the solution with nateglinide crystals, and (c) recovering the crystalline form as provided. A process for preparing crystalline form of nateglinide comprises the

precipitate The nateglinide obtained is more than about 99% pure. For example,

nateglinide (5 g) was dissolved in acetomitrile, acetone, or Et acetate at about 55° in over about 15 min until a clear solution was obtained. The solvent was removed to dryness by evaporation at about 55°,70 to 30 mmHg to give dry nateglinide crystalline Form B. Also, nateglinide Form Z was

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### 10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

prepared by treating 7.73 g of D-phenylalanine (PheoH) with 185 mL (3.5 equiv) of 3.5% NaOH at room temperature to afford a clear solution of the corresponding Na-salt. A solution of neat trans-4-isopropylcyclohexanecarboxyl chloride (IPCHAC, 9.02 g, 1.01 equiv) was added to the solution of Phe-OH obtained above, over 3 min, while stirring at room temperature. The rest of the IPCHAC in the funnel was washed with toluene (1mL) and added. The resulting mixture was stirred for 1 h, and was treated with 10% HC1 (32 mL) to adjust the HT to 3, while stirring. The mixture was stirred for 1 h, and filtered. The solid was washed with water (200 mL) and sucked well to afford 33.3 g of the moist product, which lost weight after drying at 78°/2.2 mbar (Assay 98.4%, purity >99%, yield

| L4 ANSWER 15 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2005:55192 HCAPLUS DOCUMENT NUMBER: 142:155316 A sabonification and neutralization process for the | preparation of chirally pure nategilnide from its lower alkyl esters and nateglinide polymorphic crystalline modifications | Gazdag, Maria; Gizur, Tibor; Hegedus, Bela; Szemzo,<br>Attila; Tarkanyi, Gabor; Toerley, Jozsef; Babjak,<br>Monika | Richter Gedeon Vegyeszeti Gyar Rt., Hung.<br>PCI Int. Appl., 26 pp.<br>CODEN: PIXXD2 | Patent<br>English<br>: 1   |
|---|--|--|--|--|
| L4 ANSWER 15 OF 44 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE:  |  | INVENTOR(S):   | PATENT ASSIGNEE(S):<br>SOURCE:   | DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: |

| PAT              | PATENT NO.  |      |         | KIND   | _        | DATE                |      | ~   | APPLICATION    | CATI      | NO   | NO. |     | ã        | DATE     |      |
|------------------|-------------|------|---------|--------|----------|---------------------|------|-----|----------------|-----------|------|-----|-----|----------|----------|------|
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|                  | CN,         |      | я,<br>С | G<br>G | ,<br>22  | DE,                 | Ķ    | ĕ   | , ZQ           | ည<br>임    | 띮,   | ĘĠ, | ES, | FI,      | GB,      | 9    |
|                  | GE,         |      | ₽,      | HR,    | HO,      | ID,                 | I,   | ï,  | IS,            | JP,       | Ä    | ΚĞ, | ΚP, | 8        | K2,      | ζ,   |
|                  | IK,         |      | ĽS,     | LT,    | :n,      | ΓΛ,                 | Ř,   | Š   | WG,            | Ř,        | ž    | ₹   | ž   | M2,      | NA,      | NI,  |
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|                  | TJ,         |      | E,      | TR,    | TI,      | TZ,                 | ΝA,  | ď,  | us,            | UZ,       | ζ,   | ₹   | χΩ, | 2A,      | ΖΜ,      | MΖ   |
|                  | RW: BW,     | GH,  | ₽,      | Ä      | LS,      | MΜ                  | М2,  | NA, | SD,            | SI,       | , ZS | TZ, | ug, | 2Μ,      | ΖΜ,      | AW,  |
|                  | AZ,         |      | ЖĞ,     | Κ2,    | Ď,       | RU,                 | IJ,  | Ĭ,  | AT,            | BE,       | BG,  | CH, | ჯ   | ζ2,      | ם,       | Ď,   |
|                  | EE,         |      | E,      | F.     | g,       | GR,                 | HO,  | IE, | II,            | 3         | Ř,   | N.  | PL, | PT,      | Ж,       | SE,  |
|                  | SI,         |      | TR,     | BF,    | B.7,     | CF,                 | ဗွဲ  | ü,  | ₹              | Ą         | Ŗ,   | ĝ   | ₹,  | Ä        | Ĕ        | NE,  |
|                  | SN,         |      | ŢĠ      |        |          |                     |      |     |                |           |      |     |     |          |          |      |
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| EP               | 1651591     |      |         | .A1    | •        | 20060               | 503  |     | EP 2004-743732 | 04-7      | 4373 | 2   |     | ñ        | 20040708 | 807  |
|                  | R: AT,      |      | ₽,      | DE,    | Ķ,       | , ES, FR,           | Ε,   | gB, | GR,            | II,       | ij   | E   | NĽ, | SE,      | SE, MC,  | PT,  |
|                  | IE,         | SI,  | Ľ,      | Ľ,     | FI,      | RO,                 | 5    | TR, | BG,            | CZ,       | EE,  | HO, | PL, | SK,      | H        |      |
| ns               | US 20070431 | 17   |         | Al     |          | 2007                | 222  | _   | JS 2006-5640   | -90       | 640] | _   |     | ~        | 2006051  | 515  |
| PRIORITY         | APPLN.      | INFO | ٠:      |        |          |                     |      | _   | HU 20          | 2003-2174 | 174  |     | ~   | 7        | 0030710  | 710  |
|                  |             |      |         |        |          |                     |      | _   | NO 20          | 04-1      | 1073 |     |     | <u>ة</u> | 0040,    | 0708 |
| OTHER SOURCE (S) | URCE (S):   |      |         | CASE   | EAC      | CASREACT 142:156316 | :156 | 316 |                |           |      |     |     |          |          |      |

AB The preparation of chirally pure nateglinide by treating a nateglinide lower alkyl ester (e.g., Me ester) with an alkali base (e.g., sodium hydroxide) to yield an alkali salt and neutralizing liberating the salt by addition of an acid (e.g., aqueous HCl) is described as is the preparation of polymorphic crystalline modifications of nateglainde.

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8 THERE ARR 8 CITED REFERENCES AVAILABLE FOR THIS

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ACCESSION NUMBER:
142:31704
An efficient large scale synthesis of nateglinide
TITLE:
AUTHOR (S):
Sameer J.; Galkwad, Nandakumar B.; Kulkarni, Pramila
V, Bhirud, Shekar B.
CORPORATE SOURCE:
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ACCESSION NUMBER: 2004:648495 HCAPLUS
DOCUMENT NUMBER: 2004:648495 HCAPLUS
DOCUMENT NUMBER: 141:15746 d lanine compounds as antidiabetics
TITLE: Preparation of alanine compounds as antidiabetics
Freparation of alanine compounds as antidiabetics
Shanghai Institute of Materia Medica, Chinese Academy
of Sciences, Peop. Rep. China
PCT Int. Appl., 28 pp.
DOCUMENT TYPE: Patent Rates
CODEN: PATENT NATOR COUNT: 1
PRIENT INFORMATION:

| EMIENI IN     | Š.  |  |   | KIND |   | N I   |   | -   | чи  | APPLICATION   | NOT   |   | i   | <b>a</b> i   | 3   |   |
|---------------|---|--|---|------|---|---|---|---|---|---|---|---|---|--|---|---|
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|               | ĽS,   | Ľ,   | 3   | Ľ,   | Ř   | Ã,  | MG,   | Ř   | Ä   | ξ   | Ř   | М2,   | Ň,  | NZ,  | ĕ,  | PH,   |
|               | PL,   | PT,  | 8   | RU,  | S,  | SD,   | SE,   | sg,   | SK,   | SL,   | ŢĴ,   | ĬÄ,   | ŢŇ,   | TR,  | TT,   | , ZT  |
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| RW:           | GH,   | ₹  | Ä   | ĽŠ,  | ž   | М2,   | SD,   | SI,   | , ZS  | , Z.I   | ug,   | 2M,   | ZW,   | ¥  | AZ,   | ВХ,   |
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|               | FI,   | Œ,   | 8   | GR,  | HU,   | ΙE,   | II,   | Ľ,  | Ř   | NĽ,   | PT,   | SE,   | SI,   | SK,  | TR,   | BF,   |
| -             | BJ,   | CF.  | S<br>S  | CI,  | Š   | Ą   | Ğ.  | g   | ₩   | Ä   | Æ   | Ä   | SN,   | ŢĎ,  | ΣŢ  |   |
| 0033          | 0381  |  |   | A    |   | 2004(   | 0823  |   | AU 2  | 003-  | 3038  | 15  |   | 7  | 0030  | 128   |
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|               | Ξ,  | SI,  | Ľ,  | Ľ,   | Ľ   | 80,   | Ř   | Š   | Ā,  | TR,   | BĞ,   | ,<br>22   | EE,   |  | SK  |   |
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| APPL          | . I   | NFO.   |   |      |   |   |   |   | WO 2  | 003-  | <b>96NO</b>   |   | •   | A 2  | 0030  | 128   |
| RCE (         | ::<br>60  |  |   | CASE | EAC.  | 14:   | 1:157   | 1476  | Æ.  | RPAT  | 141   | :157  | 476   |  |   |   |
|               | M: RW: RW: CO033(0033) R: | M. AE.  CO. GM. E. I.S., E. I.S., RM: GH, RM: GH, RG, E. E. E. E. D. CO0330381 E. E. D. CO051325 US. CO051325 | W: AE, AG, CC, CR, CM, HR, LIS, LIT, LS, LIT, LS, LT, LS, LT, LS, LT, LS, LT, LS, LT, LS, LT, LS, |      | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LU, LIT, LU, LG, RS, RG, RG, RG, RG, RG, RG, RG, RG, RG, RG | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LIT, LIT, LIT, LIT, LIT, LIT, LIT | AG, AL, RR, HU, LIT, LU, LIT, LU, LIT, LU, LG, RS, RG, RG, RG, RG, RG, RG, RG, RG, RG, RG | AG, AL, AM, AT, MJ, AZ, BA, CR, CC, DE, DK, DM, DZ, HR, HI, ID, LI, IN, BA, MG, MK, LIT, LU, LU, MA, MD, MG, MK, LIT, LU, LU, MA, MD, MG, MK, LIS, MM, MZ, SD, SE, SG, MG, KE, LS, MM, MZ, SD, SL, KR, MD, LT, TR, EB, CK, CG, CI, CM, CGA, CM, CG, CG, CG, CG, CG, CG, CG, CG, CG, CG | AG, AL, AM, AT, AN, AZ, BA, BB, BG, BR, BY, BZ, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, LT, LU, LD, LIN, IN, 19, PK, KG, KV, KR, KZ, LT, LU, LU, LV, MA, MD, MG, MK, MN, MM, MK, MZ, NO, PT, RO, NU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, UG, US, UZ, VC, VN, YU, ZA, ZM, ZM, CM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZM, ZM, KR, GB, CH, CT, CJ, CZ, DE, KR, GB, GG, CH, CY, CZ, DE, KR, GB, GR, HU, IE, IT, UM, MC, ML, PT, SE, SI, AI, 20041023 AU 2003–303815  AI, 20041023 AU 2003–303815  AI, 20041023 EP, 2003–815509  BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, LY, SI, KD, MK, CY, AL, TR, BG, CZ, EE, SI, LI, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SI, LI, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SI, LI, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SI, LV, LV, LV, LV, LV, LV, LV, LV, LV, LV | HG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CR, CZ, DE, DK, DW, DZ, CC, EE, ES, FT, GB, GB, GD, LU, LU, LU, LU, LU, LM, HD, MG, MK, MN, MM, MK, MZ, NO, NZ, LT, LU, LU, LV, MA, MD, MG, MK, MN, MM, MK, MZ, NO, NZ, PT, RS, RS, SL, TJ, TM, TN, TR, MG, MK, SL, LJ, TM, TN, TR, MG, MK, MZ, SD, SL, SZ, TZ, UG, ZM, ZM, AM, MZ, SD, SL, SZ, TZ, UG, ZM, ZM, AM, NG, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZM, ZM, AM, NG, LS, MM, MZ, MD, SD, SL, SZ, TZ, UG, ZM, ZM, AM, NG, LS, MM, LE, SD, ST, SE, SD, SK, CC, CG, CC, CM, CG, CM, ML, MK, NE, SN, TD, SD, SD, SD, SD, SD, SD, SD, SD, SD, S |

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10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

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AB Alanine compds. I (R1 = H, alkyl, Ph, aryl, heteroaryl, etc.; R2 = H, alkyl), useful for treatment of type II diabetes, are prepared Thus, (2S)--2-(N-trans-4-isopropylcyclohexylcarbonyl)aminoj-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionic acid was prepared and showed insulin sensitizer activity.

insulin sensitizer activity.

L4 ANSWER 18 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
CCCSSION NUMBER: 2004:203799 HCAPLUS
DOCUMENT NUMBER: 140:241062
TITLE: Process for the formation of a crystalline polymorphic form of nategalinide
INVENTOR(S): Process for the formation of a crystalline polymorphic form of nategalinide
FATENT ASSIGNEE(S): Process for the formation of a crystalline polymorphic form of nategalinide
FATENT ASSIGNEE(S): Process for the formation of a crystalline polymorphic form of nategalinide
FATENT ASSIGNEE(S): Reddy's Laboratories Limited, India; Reddy's Laboratories Limited, India; Reddy's Laboratories Limited, India; Reddy's CODEN: PIXXD2
DOCUMENT TYPE: CODEN: PIXXD2
DOCUMENT TYPE: CODEN: PIXXD2
FAMILY ACC: NUM. COUNT: 1
PARENT INFORMATION:

, DK, EE, ES, DK, EE, ES, SN, TB, TG, 20020828 20030827 A 20030827 W 20030827 20030827 CA, CH, CN, GD, GE, GH, LC, LK, LR, NO, NZ, OM, TJ, TM, TN, BZ, KZ, NI, SY, SY, SE, NE, IN 2002-MA631 AU 2003-262928 US 2003-649380 IN 2002-MA631 WO 2003-US26880 WO 2003-US326880 APPLICATION NO. SE TAG BA, BB, B DZ, EC, B JP, KE, B MK, MN, D SD, SE, S VC, VN, SL, S SL, SZ, SZ, S LU, MC, B GN, GQ, G 20040311 AT, DE, KIND AH, CZ, CZ, IID, IID, UA, UA, UA, CG, CG, AA WO 2004020396 PATENT NO.

AB A crystalline polymorphic form of nateglinide are described and its X-ray diffraction pattern presented.

Page 46 searched 5/2/07

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Gozlan, Yigael; Gome, Boaz
Teva Pharmaceutical Industries Ltd., Israel; Teva
Pharmaceutical Usa, Inc.
PCT Int. Appl., 130 pp.
CODDN: PIXKDZ TA E. E. E. BY, 20030718 20030812 CA, CH, GD, GE, LC, LK, NO, NZ, TJ, TM, AM, AZ, BZ, KZ, NI, SY, ZW, BY, FI, KR, SL, SL, WO 2003-US22375 APPLICATION NO. APPLICATION NO. WO 2003-IB3270 14 ANSWER 21 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:80637 HCAPLUS DOCUMENT NUMBER: 140:151932 BG, KG, KG, YU, BB, EC, KE, KE, VN, 20040129 AU, AZ, I DK, DM, I IN, IS, MD, MG, I RU, SC, US, UZ, MZ, SD, 20040304 KIND D A1 A1, CZ, DE, ILV, MA, PT, RO, UG, UG, UG, LS, MW, LS, MW, LS, MW, English 1 English Patent KIND Al AM, CZ, CZ, IID, IV, PT, UA, UA, GR, CG, WO 2004018408
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CO, CR, CU,
CM, HR, HU,
EM, HT, II, IV,
PG, PH, PL,
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RWI CH, CM, KE,
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FI, FR, CB,
FI, FR, FR, FR, FR,
FI, FR, FR, FR,
FI, FR, FR, FR,
FI, FR, CB,
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FI, FR, CB,
FI, FR, FR,
FI, FR, FR,
FI, FR, CB,
FI, FR, FR,
FI, FR, FR,
FI, FR, FR,
FI, FR, LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: M: AE, AG, F CO, CR, C GM, HR, F LS, LT, I PG, TR, TT, I RW: GH, GM, F PATENT ASSIGNEE(S): WO 2004009532 PATENT NO. PATENT NO. DOCUMENT TYPE: TITLE: INVENTOR(S): SOURCE:

Page 48 searched 5/2/07

searched 5/2/07

Page 47

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|---|---------------------------------|
| SE, SE, SS, TR, SE, SI, TR, SE, SI, TR, 20030718 20030718 20030718 20030718 20030718 20030718 20030718 20030718 20030718 20030718 20030718 20030718 20040113 20040113 ES, FI, GB, GD, KK, KK, LC, KK, | A 20031224<br>W 20040113        |
| HE BE   | US 2003-746697<br>WO 2004-US839 |
| TJ, TM, AT, THO, CK, CK, CK, CK, CK, CK, CK, CK, CK, CK   | 4                               |
| KG, KZ, MD, RU, EI, FR, GB, GR, 52782 53 84 53 84 53 84 53 89 64 65 65 66 67 67 67 67 67 67 67 67 67 67 67 67   | , , , , , , , , , , , , , , ,   |
| KG, K<br>EI, F<br>EV, E<br>CA 2492643<br>CA 2492643<br>AU 2003253971<br>US 2003253971<br>US 2003014959<br>US 200301499<br>US 200301499<br>US 200301499<br>US 200301499<br>WO 2004067496<br>WO 2014067496<br>WO 2014067496   | or the ore                      |

searched 5/2/07

Page 49

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

ä OTHER SOURCE(S): CASREACT 140:94292

AB A process for the preparation of nateglinide involves converting trans-4-isopropylcyclohexanecarboxylic acid into the acid chloride by reaction with thionyl chloride in the presence of an organic amide and acylation of a suitable salt of D-phenylalanine with the acid chloride a single or two phase system or in water free of a co-solvent.

A1 20030718

US 2003-622999

| 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT | 44 HCAPLUS COPYRIGHT 2007 ACS on STN 2003:892741 HCAPLUS 1393:80757 Process for the preparation of a crystal polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide) Rajamhendra, Shammuphasamy, Aswathanarayanappa, Chandrashekar; Puthiaparampil, Tom Thomas; Sridharan, Madhavan; Ganesh, Sambasivam 1): PCT Int. Appl., 19 pp. CODEN: PIXXD2 PAT INT. Appl., 19 pp. English COUNT: 1 | D DATE APPLICATION NO. | A1. 20031133 W0 2002-IN114  A26, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CZ, DE, NE, NP, DZ, EE, ES, FI, GB, GD, GE, GB, GB, GB, GB, GB, GB, GB, GB, GB, GB |
|--|--|------------------------|---|
| REFERENCE COUNT:   | g  | PATENT NO.             | AL, OU, DU, DU, DU, DU, DU, DU, DU, DU, DU, D   |

Page 51 searched 5/2/07

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Page 52

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

| DATE  20030414 CA, CH, CN, GD, GE, GH, LC, LK, LR, NO, NY, OM, TN, TR, TT, AM, AZ, BY, SI, SK, TR, SI, SK, TR, SV, TD, TG 20030414 SE, MC, PT, HU, SK A 20020415 W 20030414 SI, SM, SM, SM, SM, SM, SM, SM, SM, SM, SM | hibiting high solubility for poor solubility for poor solubility for solvent comprising a le and a solvent exhibiting the resulting nateglinide product to filtration, and a known antidiabetic.  RENCES AVAILABLE FOR THIS VAILABLE IN THE RE FORMAT   | de salts<br>d'Victor;<br>bh   | DATE<br>20030310<br>CA, CH, CN,<br>GD, GE, GH,  |
|--|---|---|---|
| KIND DATE APPLICATION NO.  1. 20010123 WO 2003-194686  1. AM, AT, AU, AZ, BA, BB, BB, BB, BB, BB, BB, BB, BB, BB   | preaks: 4.8, 5.3", 14.3", 15.2" (2 theral) of nateglinide, which are all novel crustals, can be prepared by a method comprising dissolving nateglinide in a solvent exhibiting high solubility for nateglinide and then adding a solvent exhibiting poor solubility for nateglinide or dissolving nateglinide in a mixed solvent comprising a solvent exhibiting high solubility for nateglinide and a solvent exhibiting poor solubility for nateglinide and a solvent exhibiting solution to precipitate crystals, subjecting the product to filtration, and drying at a specific temperature Nateglinide is a known antidiabetic.  Output of the precipitate crystals, subjecting the product of solutions and drying at a specific temperature Nateglinide is a known antidiabetic.  RECORD. ALL CITATIONS AVAILABLE FOR THIS RECORD. | 44 HCAPLUS COPYRIGHT 2007 ACS on STN 2003:73716 HCAPLUS 139:230996 Preparation and properties of nateglinide Stuton, Paul Allen, Vivilecchia, Richard Parker, David John; De La Cruz, Marilyn Novartis Ag, Switz.; Novartis Pharma Gmbh CODEN: PIXXD2 CODEN: PIXXD2 Patent English COUNT: 1 | KIND DATE APPLICATION NO.  A1 20030918 W0 2003-EP2447 G, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, R, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, |
| PATENT NO.  WO 200387039  W: AE, AG, A  C, CR, C  CO, CR, C  GM, HR, H  LI, PL, P  EN, PL, P  FI, FW, CM, U  FI, FW, CM, CM, U  FI, FW, EN, CM, CM, CM, CM, CM, CM, CM, CM, CM, CM                                     | peaks: 4.8", nateglinide, comprising di nateglinide a nateglinide a solvent exhib poor solubili solution to b then drying at a s REFERENCE COUNT:   | L4 ANSWER 25 OF 4 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. CC PATENT INFORMATION:   | PATENT NO   |

| JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, NI, NO, NZ, OW, PH, PL, PT, RO, RU, SC, TR, TT, UA, US, UZ, VC, WY, YU, ZA, ZW RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, | 18 CA 2003-2478599 20030310 22 AU 2003-214112 20030310 38 EP 2003-709769 20030310 54 GB, GR, IT, LI, LU, NL, SE, MC, PT, K, CY, AI, TR, RG, CZ, EE, HIL SK, CY, AI, TR, CY, CY, CY, CY, CY, CY, CY, CY, CY, CY | 28 BR 2003-8316 20030310 27 JP 2003-574615 20030310 20 CN 20003-805803 20030310 20 US 2004-507255 20040928 US 2002-363178P P 20020311 WO 2003-EP2447 W 20030310 | The invention relates to salts of nateglinide having specified properties (m.ps., solubilities, X-ray diffraction patterns) for use in pharmaceutical compns. For preventing or treating diabetes, cardiovascular diseases, etc. Nateglinide Na, K, Ca, Mg, N-methyl-D-glucamine, TRIS, lysine, and ammonium salts were prepared and their properties tabulated.  STHEER ARE 3 (TIED REPERNICES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT  |
|--|--|---|--|
| HX, MY<br>HX, NT<br>HB, HB, HB, HB, HB, HB, HB, HB, HB, HB,  | 20030918<br>20030922<br>20041208<br>ES, FR, C  | 20041228<br>20050707<br>20050720<br>20051020  | diffred diffrent revent Na, K, ere presere preserves prese |
| KZ, H,   | 7K 22  | 8888  | sal<br>ray<br>for p<br>ide<br>ide<br>trs w<br>TH   |
| IL,<br>TJ,<br>KG,<br>FI,   | A1<br>A1<br>DE,  | APAR  | es to<br>1, X-<br>1s. f<br>eglin<br>a sal  |
| SK, MD,  | CH,  | ·   | elate<br>ities<br>compr<br>Nate<br>onium   |
| AA,  | 31.)<br>BE,<br>ST.   | 16<br>49<br>29<br>INFO  | on roubil:   |
| HR,<br>LV,<br>SE,<br>RW: AM,<br>DK,  | CA 2478599<br>AU 2003214112<br>EP 1483232<br>R: AT, BE, CH   | BR 2003008316<br>JP 2005519949<br>CN 1642904<br>US 2005234129<br>PRIORITY APPLN. INFO.:   | AB The inventi<br>(m.ps., sol.<br>pharmaceuti<br>diseases, e<br>lysine, and<br>REFERENCE COUNT:  |
|  |  | PRIO  | AB<br>REFE   |

| L4 ANSWER 26 OF 44      | L4 ANSWER 26 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN |
|-------------------------|--|
| ACCESSION NUMBER:       | 2003:76738 HCAPLUS                                   |
| DOCUMENT NUMBER:        | 138:137033   |
| TITLE:                  | Oxidative process and catalysts for the manua        |
|                         | para-substituted benzoic acids from their            |
|                         | corresponding aldehydes                              |
| INVENTOR(S):            | Girgis, Michael John; Shekhar, Ratna                 |
| PATENT ASSIGNEE(S):     | Novartis AG, Switz.                                  |
| SOURCE:                 | PCT Int. Appl., 15 pp.                               |
|                         | CODEN: PIXXD2  |
| DOCUMENT TYPE:          | Patent   |
| LANGUAGE:               | English  |
| FAMILY ACC. NUM. COUNT: | : 1  |
| PATENT INFORMATION:     |  |

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| PAT      | PATENT NO.            |       |     | KIND |     | DATE     |        | 1   | PPLI         | CAT      | APPLICATION NO. | ç   |     | ă        | DATE     |     |
|----------|-----------------------|-------|-----|------|-----|----------|--------|-----|--------------|----------|-----------------|-----|-----|----------|----------|-----|
| i C      | WO 2003008367         | 367   |     | 128  |     | 0030130  | 130    |     | WO 2002-US22 | 02-1     | WO 2002-US22631 | 331 |     | iδ       | 20020716 | 91  |
| 03       | 2003008367            | 367   |     | æ    |     | 2003     | 0410   |     |              |          |                 |     |     |          |          |     |
|          | W: AE                 | , AG, | AL, | AM,  |     | AU,      | A2,    |     | BB,          | ,<br>BG, | BR,             | BY, | В2, | ð        | G,       | S,  |
|          | 8                     | g,    | 8   | CZ,  |     | Ķ,       | M<br>M |     | ည<br>임       | 띮,       |                 | FI, | 8   | 9        | ĜE,      | GH, |
|          | æ                     | , HR, | HO, | ID,  |     | IN,      | IS,    |     | Ä,           | χ,       |                 | Ř,  | K2, | ដ        | ř        | ĽŖ, |
|          | ST                    | LT,   | LU, | ĽV,  |     | ÄĎ,      | MG,    |     | ₹            | ₹        |                 | MZ, | Š,  | ,<br>2N  | δ<br>Θ   | PH, |
|          | PL, PT                | , PT, | ВО, | RU,  | SD, | SE,      | SG,    | SI, | SK,          | SI,      |                 | Ĭ,  | ī,  | Ę,       | TT,      | 1Z, |
|          | UA                    | , UG, | us, | 02,  |     | χΩ,      | 2A,    | ΖΜ, | <b>%</b> 2   |          |                 |     |     |          |          |     |
|          | RW: GH                | ₽,    | ĸE, | ĽS,  |     | М2,      | SD,    | SI, | , 2S         | , ZT     | ď,              | ZM, | ZM, | Æ        |          | ВХ, |
|          | KG                    | , K2, | ð   | RU,  |     | Ξ        | AT,    | BE, | BG,          | Œ,       | 5               | CZ, | Ē,  | Ķ        |          | ES, |
|          | E                     | Ε,    | gB, | gB,  |     | II,      | ĽŪ,    | ÃĊ, | NT,          | PT,      | SE,             | SK, | TR, | BF,      | BJ,      | ĊF, |
|          | 90                    | CI,   | S   | GA,  |     | g        | ĞW,    | ÄĽ, | ₩,           | Ä,       | SN,             | TD, | ŢĠ  |          |          |     |
| ns       | 2003023               | 115   |     | Al   |     | 20030    | 130    | ٠   | 15 20        | 02-1     | US 2002-196600  | 0   |     | 7        | 20020715 | 15  |
| ns       | 6740776               |       |     | B2   | .,  | 20040    | 525    |     |              |          |                 |     |     |          |          |     |
| AU       | AU 2002313681         | 681   |     | A1   |     | 20030303 | 303    | 4   | M 20         | 05-3     | AU 2002-313681  |     |     | ~        | 20020716 | 16  |
| PRIORITY | PRIORITY APPLN. INFO. | INFO  | ٠:  |      |     |          |        | د   | 15 20        | 6        | 10564           | 8 P | _   | <u>ج</u> | 00100    | 16  |
|          |                       |       |     |      |     |          |        | 35  | 20           | 1-20     | 15226           | 53  | •   | 2        | 70207    | 16  |

Page 53 searched 5/2/07

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

OTHER SOURCE(S): CASREACT 138:137033, MARPAT 138:137033
AB A low-temperature process for preparing aromatic acids 4-(R1R2CH)C6H4CO2H [R1, R2 = H, C1-8 (un)branched alkyl, cycloalkyl; e.g., 4-isopropylbenzoic acidl comprises oxidizing the corresponding aromatic aldehyde 4-(R1R2CH)C6H4CHO (e.g., 4-isopropylbenzaldehyde) with a gas having an oxygen content of 1-100% at 20° to <100° in the presence of a supported Group VIII metal catalyst (e.g., Pt/C), and using a solvent having a flash point >95°C and/or a m.p. <55°, provided that the flash point of the solvent is greater than the reaction temperature

ACCESSION NUMBER: 2003:62632 HCAPLUS
DOCUMENT NUMBER: 138:73015
TITLE: 138:73015
TITLE: Synthesis process for trans-4isopropyl, cyclohexanecarboxylic acid
Gu, Lianquan; An, Linkun; Ma, Lin; Guo, Xindong;
Hang, Zhishu
PATENT ASSIGNEE(S): Raming Zhuanli Shenqing Gongkai Shuomingshu, 6 pp.
CODEN: CODEN: CXXEV
DOCUMENT TYPE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

CN 1319583
A 20011031 CN 2001-107459

PRIORITY APPLN. INFO.: CASREACT 138:73015
AB The process comprises hydrogenating cumic acid in acetic acid in the presence of PtO2, recovering solvent, treating with 10-35% inorg. base (such as Ba(GH)2, Mg(GH)2, KOH, or NaOB) solution at 50-150° for 10-20 h neutralizing with HCl to pH 2, crystallizing, filtering, and recrystg. in methanol.

methanol.

14 ANSWER 28 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
CCCESSION NUMBER: 139:210299
DOCUMENT NUMBER: 2003:30017 HCAPLUS
DOCUMENT NUMBER: 139:210299
Study on separation of cis-isomer of nateglinide by Study on separation of cis-isomer of nateglinide by AUTHOR(S): Yan, Xiaoyan; Hu, Xin; Cao, Guoying; He, Xiaocong; Yin, Qi CORPORATE SOURCE: Beljing Hospital, Ministry of Public Health, Beijing, 100730, Peop. Rep. China 2hongquo Yaoxue Zazhi (Beijing, China) (2002), 37(6), 444446
DOCUMENT TYPE: Journal Choral Cazhishe DOCUMENT TYPE: Journal Choral Chinese AB A high-pressure liquid chromatog, method for the separation of cis-isomer of nateglinide was established on Phenomenex Luna C18 column (5 µm, 4.6 mm x 250 mm) with UV detection at 214 nm and room temperature The mobile phase

was consisted of (A) acetonitrile and (B) 0.03 mol L-1 phosphate buffer (pH 2.5, 65:35, volume/volume). The resolution factors were at least 1.5. The limits of detection and quantitation limit was 0.06 and 0.18 μg mL-1,

Page 54 searched 5/2/07

resp. The method is useful in separation and determination of the cis-isomer nateglinide. from

a new synthesis method of nateglinide as antidiabetic Wang, Dun; Liang, Yiheng; Gong, Ping; Zhao, Yanfang School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop. Zhongquo Yaowu Huaxue Zazhi (2002), 12(2), 94-96 CODEN: ZYHZEF; ISSN: 1005-0108 Zhongquo Yaowu Huaxue Zazhi Bianjibu PLUS COPYRIGHT 2007 ACS on STN 2002:609152 HCAPLUS Rep. China 138:254901 Chinese Journa L4 ANSWER 29 OF 44 HCAPLUS
ACCESSION NUMBER: 2002:6
DOCUMENT NUMBER: a new DOCUMENT TYPE: LANGUAGE: OTHER SOURCE(S): AB A new antidia AUTHOR(S): CORPORATE SOURCE: PUBLISHER:

CASTRECT 138:254901
A new antidiabetic drug-nateglinide was synthesized from isopropylbenzene
A new antidiabetic drug-nateglinide was synthesized from isopropylbenzene
to obtain trans-4-isopropylhexanecarboxylic acid, acylation of
D-phenylalanine Et ester, hydrolysis to obtain nateglinide B-type crystal,
and crystal-conversion. The total yield was 9.8%.

Process for producing B-form nateglinide crystals Sumikawa, Michito; Maruo, Makoto; Miyazaki, Kazuo; Nishina, Shigehiro; Matsuzawa, Yukiko Ajinomoto Co., Inc., Japan CoT Int. Appl., 9 pp. CODEN: PIXXD2 ANSWER 30 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN SION NUMBER: 2002:332157 HCAPLUS ENT NUMBER: 136:340998 Japanese PATENT ASSIGNEE (S): L4 ANSWER 30 OF ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: DOCUMENT TYPE: INVENTOR(S): SOURCE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

CA, CH, CN, GD, GE, GH, LC, LK, LR, NZ, PH, PL, TZ, UA, UG, 20011023 20011023 20011023 CH, CY, TR, BF, TG SE, MC, PT 20011023 20011023 SE, TD, RZ, TT, SY, Ä GB, GR, IT, LI, LU, N CY, AL, TR S 2001-14846 BU 2003-111948 US 2003-211888 AU 2001-96001 CA 2001-2426745 EP 2001-976819 ZW, NE, TA, KA, APPLICATION NO. WO 2001-JP9293 KES, KY, KE, 12, M. KU, EE, KG, TJ, SL, SZ, 7 IE, IT, 1 GO, GW, 1 SE, KE, MZ, SD, GB, GR, GA, GN, 20020506 20030423 20030813 20040225 20060427 20031211 AZ, DM, IS, MG, SI, ES, FR, RO, MK, 0020502 BE SG, DE, FY, 495435433 884833 £, AT, BE, L IE, SI, L BR 2001014846 RU 2275354 US 2007 AU 200196001 CA 2426745 EP 1334964 PATENT NO.

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

20050415

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IN 2003CN00609

AB A process for producing B-form nateglinide crystals containing substantially no H-form crystals comprises the steps of drying wet crystals of a nateglinide solvate at a low temperature until the solvent disappears and then causing them to undergo a crystal transition. Nateglinide is a known antidiabetic. By this process, B-form nateglinide crystals can be produced on an industrial scale.

REFERENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE FOR THIS RECORD. Process for producing nateglinide crystals
Takahashi, Daisuke; Nishi, Selichi; Takahashi, Satoji
Ajinomoto Co., Inc., Japan
PCT Int. Appl., 14 pp.
CODEN: PIXXD2 20030424 A 20001024 W 20011023 IN 2003-CN609 JP 2000-324375 WO 2001-JP9293 COPYRIGHT 2007 ACS on STN 44 HCAPLUS COPYRIGHT 2007 2002:314896 HCAPLUS 136:325825 Japanese Patent FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PRIORITY APPLN. INFO.: PATENT ASSIGNEE (S): L4 ANSWER 31 OF ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): SOURCE:

CA, CH, CN, GD, GE, GH, LC, LK, LR, NZ, PH, PL, TZ, UA, UG, BE, CH, CY, SE, TR, BF, TD, TG 20011016 20011016 SE, MC, PT, 20011016 20011016 20011016 20011017 20030411 20030418 20011016 20011016 20011016 20011016 20001018 a a a GB, GR, IT, LI, LU, NL, SI, CY, AL, TR 4 BR 2001-14729 6 CN 2005-11021 1 TW 2001-9125697 1 TW 2003-0125697 2 US 2003-418105 BZ, GB, NO, TT, AT, PT, SN, AU 2001-94265 CA 2001-2425538 EP 2001-974875 UG, ZW, MC, NL, MR, NE, BY, FI, KR, MZ, JP 2000-317604 CN 2001-820658 WO 2001-JP9069 APPLICATION NO. SZ, TZ, IT, LU, GW, ML, EE, KG, TJ, SI, DK, ES, FR, (FI, RO, MK, (20031014) 20060410 20060310 2006032 20050415 20040212 20020425 AU, AZ, DK, DM, IN, IS, MD, MG, I SG, SI, MZ, SD, GB, GR, GA, GN, CA, GN, CO20020429 20030410 20030813 20070424 GB, KW, KB, KIND 49838433 BR 2001014729
RN 2273829
CN 1769263
TW 251388
IN 2003CN00537
US 2004030182
US 7208622
PRIORITY APPLN. INFO.: AE, AG, CO, CR, GM, HR, FLS, LT, PT, RO, US, UZ, GH, GM, BJ, CF, R: AT, BE, IE, SI, AU 200194265 CA 2425538 EP 1334963 WO 2002032854 PATENT NO. RM:

A process for producing nateglinide crystals comprises reacting trans-d'isoprophicyclohexylcarbonyl chloride with Dephenylablanine in a mixed solvent consisting of a ketone solvent and water in the presence of an alkali to obtain a reaction mixture containing nateglinide, adding an acid CASREACT 136:325825 OTHER SOURCE(S): B

the reaction mixture to make it acidic, and regulating (a) the temperature to ç

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Page 55

 $58^{\circ}$  to 72° and (b) and the ketone solvent concentration to > 8 weights and < 22 weights, to conduct crystallization Nateglinide is a known

The process is an industrially advantageous method for crystallizing nateglinide.

REFERENCE COUNT: 4 THERE ARE 4 CITER DEPENDENCE NATIONAL PROPERTY.

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Process for preparation of acylphenylalanines Sumkawa, Michito; Ohgane, Takao Ajinomoto Co., Inc., Japan PCT Int. Appl., 14 pp. CODEN: PIXXD2 PLUS COPYRIGHT 2007 ACS on STN 2002:314895 HCAPLUS 136:340997 Japanese 1 Patent HCAPLUS FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L4 ANSWER 32 OF 44 ACCESSION NUMBER: PATENT ASSIGNEE(S): DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): SOURCE:

BE, CH, CY, SE, TR, BF, TD, TG CA, CH, CN, GD, GE, GH, LC, LK, LR, NZ, PH, PL, TZ, UA, UG, 20011016 20011016 20011016 SE, MC, PT, 20011016 20011016 20011017 20030411 20030418 20011016 20051228 9 AU 2001-94264 0 CA 2001-942533 1 EP 2001-974874 1, CB, CR, II, LU, NL, SI (CY, AL, TR 2001-912695 10 TW 2003-111012 11 TW 2003-012695 15 US 2003-418102 RZ, KZ, TT, AT, PT, SN, BR, BY, ES, FI, KP, KR, MX, MZ, TM, TR, UG, ZW, MC, NE, MR, NE, US 2005-319177 JP 2000-317603 WO 2001-JP9068 US 2003-418102 APPLICATION NO WO 2001-JP9068 ¥5,73 EE, KEE, SL, SZ, IE, IT, GQ, GW, I 88, K, YE, SK, MZ, SD, GB, GR, GA, GN, 20020429 20030410 20030813 20031014 20061120 20040211 20050415 20040205 AZ, DM, IS, MG, SI, ES, FR, RO, MK, 20020425 꽃, AT, III, MA, ZA, MW, GM, 0320...
A AL. A
CO, CR, CU, C
CM, HR, HU, C
LS, LT, LU,
PT, RO, RU,
PT, RO, RU,
VS, UZ, VN
RW: GH, GM, KF
BJ, CF, C
JJ 200194264
LJ 2425533
EP 1334962
EP 1334962 ; ; BR 2001014728
RU 2287520
TW 57541
IN 2003CN00536
US 2004C2419
US 7030C88
US 2006155143
PRIORITY APPLN. INFO.: R: AT, BE, C IE, SI, I 2001014728 WO 2002032853 PATENT NO. E & E

This document discloses a process for preparing easily and simply high-purity acylphenylalanines extremely useful as raw materials of furgs or the like, characterized by reacting an acid chloride with phenylalanine in a mixed solvent consisting of an organic solvent and water under conditions made A 20001018 W 20011016 A1 20030418 CASREACT 136:340997 OTHER SOURCE(S): AB This documer

alkaline

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT with potassium hydroxide. REFERENCE COUNT: 7

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searched 5/2/07 Page 57

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

Drugs for diabetes, especially type 2, comprising an antiinflammatory or analgesic drug, selected bivalent linkers, and a nitrate ester bel Soldato, Piero Nicox S.A., Fr. PCT fir. Appl., 66 pp. CODEN: PIXXD2 2002:293592 HCAPLUS 136:325420 INVENTOR(S): PATENT ASSIGNEE(S): ACCESSION NUMBER: DOCUMENT NUMBER: TITLE:

SOURCE:

Patent English DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

s, CH, CY, s, TR, BE, 5, TG 20001012 20011009 20011009 20011009 SE, MC, PT, 20030411 20001012 20011009 72, 14, 20011009 20011009 CU, IC, SK, ST, ĭ, CA 2001-2425655 AU 2002-14006 EP 2001-982414 J. CB., IT, LI, LU, JP 2002-534256 US 2003-398511 IT 2000-MIZ201 WO 2001-EP11665 WO 2001-EP11665 APPLICATION NO. ζ, Ω, ES, FR, G, RO, MK, C, 20040415 20020412 20030926 20020418 20020422 20030709 20020418 BG, NO, SD, SD, GR, 20040205 9.6 K K K 15.8 ï, ₽, E, E, Ø, a e e e KIND A2 A3 AU, YU, YU, CI, CI, A1 A1 A2 A2 LV, 41 A1 G S K K K G K ĘŻ PRIORITY APPLN. INFO.: AE, AG, EE, GD, LV, MA, US, UZ, GH, GM, DE, DK, BJ, CF, R: AT, BE, IT 2000MI2201 IT 1319201 CA 2425655 AU 200214006 EP 1324974 WO 2002030867 WO 2002030867 JP 2004511456 2004023890 PATENT NO. RW:

H

MARPAT 136:325420

OTHER SOURCE(S):

G

6 Useful for the treatment of diabetes, particularly type 2, are compds. On salts thereof, having the following general formula A + (B)n + (D)n + (D)ΑB

complications of diabetes, particularly vascular diseases, rethnopathies, neuropathies, etc. The values of n and m, i.e., the presence or absence of bivalent linkers B and C, alone or in combination, are based on performance of the precursors of the linkers in certain tests (no data). These tests are designated as follows: (test 4A): inhibition by > 15% of hemolysis of rat erythrocytes induced by cumene hydroperoxide; (test 5): inhibition of radical production by > 50% in the oxidative degradation of desoxyribose in aqueous Fe2+(NH4)2(SO4)2/thiobarbituric acid solution; and insulin. I increase the direct antidiabetic effect of insulin, and reduce (test

4): inhibition by 2 50% of DPPH-induced radical production in MeOH solution For instance, acetylsalicylic acid chloride was esterified with 3-(hydroxymethyl)phenol (80%), followed by nitation of the resultant Ph ester with HNO3/HS204 (82%), to give invention compound II, which is thus the 3-(nitrooxymethyl)phenyl ester of aspirin. When tested on isolated aorta from insulin-resistant rats, compound II at a concentration of 10-4 M gave

effect was unchanged by the presence or absence of the irreversible NO synthetase inhibitor LNNA. In contrast, both Na nitroprussiate and the indomethacin analog of II, known NO donors, were inactive, and the antidiabetic drug metformin was inactivated by LNNA. This 70% vasorelaxation, relative to non-insulin-resistant controls.

SUCALLY, STATE OF THE STATE OF THE STATE OF THE STATE OF THE STAPE OF HCAPLUS COPYRIGHT 2007 ACS on STN 2002:174779 HCAPLUS ANSWER 34 OF 44 L4 ANSWER 34 OF ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: CORPORATE SOURCE: AUTHOR(S):

Hanover, NJ, USA Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000 (2001), Meeting Date 2000, 228-231. Editor(s): Pleiss, Ulrich; Voges, Rolf. John Wiley & Sons Ltd.: Chichester, UK. CODEN: 69CIJC; ISBN: 0-471-49501-8

SOURCE:

CASREACT 137:370326 Conference English LANGUAGE: OTHER SOURCE(S): AB A novel oral DOCUMENT TYPE:

A novel oral medication for treating type 2 diabetes is trans—N-[(4-(1-methylethyl)cyclohexyl]—carbonyl]—D-phenylalanine, DN608 [Starlix]. The key step in the synthesis of [14(JDN608 was the catalytic reduction of [carboxy-14(]cund caid in the presence of RtO2 at 55 psi of hydrogen in acetic acid to give cis/trans-4-isopropylcyclohexane—[14(]carboxylic acid in 3:1 ratio. Alternatively methods for preparing this mixture of cis- and trans- acids (3:1) are presented. Tritiated DN608 was prepared by reduction of the corresponding chloro derivative with tritium gas

III DESENCE Of 10% palladium on carbon.

REFERENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT

in the

COPYRIGHT 2007 ACS on STN HCAPLUS ANSWER 35 OF 44 L4 ANSWER 35 OF ACCESSION NUMBER: DOCUMENT NUMBER:

2002:130037 HCAPLUS
137:325603
Synthesis of Nateglinide
Zhu, Kwe-yan, Peng, Ka; Wang, Xiao-qin, Yang, Li-ping
Dep. Chem., East China Normal Univ., Shanghai, 200062, AUTHOR(S): CORPORATE SOURCE:

searched 5/2/07 Page 59

## 10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

(SOURCE(S):Title compound, a new antidiabetes medicine, was synthesized from iso-propylbenzene in seven steps, giving the product with overall yield Hecheng Huaxue (2001), 9(6), 537-540 CODEN: HEHUE2; ISSN: 1005-1511 Hecheng Huaxue Bianjibu Peop. Rep. China Chinese Journal iso-propylbenzene OTHER SOURCE (S) : . DOCUMENT TYPE: PUBLISHER: LANGUAGE: Ð

Preparation and effect of cycloalkylcarboxamide derivatives as cysteine protease inhibitors Sato, Masaaki; Mukoyama, Harunobu, Kobayashi, Junichi; Tsuyuki, Shogo; Tovitake, Katsunori; Akabane, Satoshi Kissei Pharmaceutical Co., Ltd., Japan Jpn. Kokai Tokkyo Koho, 27 pp. HCAPLUS COPYRIGHT 2007 ACS on STN 2001:38482 HCAPLUS CODEN: JKXXAF 134:100592 Japanese COUNT: L4 ANSWER 36 OF 44 ACCESSION NUMBER: PATENT ASSIGNEE(S): FAMILY ACC. NUM. CC PATENT INFORMATION: DOCUMENT NUMBER DOCUMENT TYPE: INVENTOR (S): SOURCE:

LANGUAGE:

19990701 19990701 APPLICATION NO. JP 1999-188275 JP 1999-188275 MARPAT 134:100592 20010116 K PRIORITY APPLN. INFO.: OTHER SOURCE(S): GI JP 2001011037 PATENT NO.

-CONH-CH-CO-COZR3

Title compds. [1, R1 = alkyl; Y = alkylene; R2 = OH, aryl, aryl alkoxy; R3 = H, alkyl, aryl, pyridyl, arylalkyl, pyridylalkyl; Z = O, NH; n = integer 1-3 and stereoisomers are prepared and possesses the cysteine protease inhibitory effect. Title compds. are useful in prevention of arthritis, Alzheimer's disease, rheumatism and osteoporosis. Thus, the title compound II was prepared and tested. ΑB

Hybridization of non-sulfonylurea insulin secretagogue and thiazolidinedione-derived insulin sensitizer Kitajima, Hiroshi; Nakamura, Mitsuharu; Tamakawa, Hiroki; Goto, Nobuharu
Department of Discovery Research, Welfide Corporation,
Hirakata, 573-1153, Japan
Bioorganic & Medicinal Chemistry Letters (2000),
10(21), 2433-2456
CODEN: BMCLE8; ISSN: 0960-894X HCAPLUS COPYRIGHT 2007 ACS on STN 2000:840649 HCAPLUS 134:110109 ANSWER 37 OF 44 L4 ANSWER 37 OF ACCESSION NUMBER: CORPORATE SOURCE: DOCUMENT NUMBER AUTHOR(S): SOURCE: TITLE:

Elsevier Science Ltd. DOCUMENT TYPE: LANGUAGE: GI PUBLISHER:

thiazolidinedione-derived insulin-sensitizing agents were designed and synthesized. The benzylidenesuccinic acid derivative I was equal both to nateglinide in potency of insulin-releasing activity and to pioglitazone in insulin-sensitizing activity.

19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT Hybrid compds. of non-sulfonylurea insulinotropic agents and REFERENCE COUNT: Æ

COPYRIGHT 2007 ACS on STN 1997:228845 HCAPLUS 126:220267 HCAPLUS ANSWER 38 OF 44 L4 ANSWER 38 OF ACCESSION NUMBER: DOCUMENT NUMBER: TITLE:

Extructure determination of metabolites isolated form urine and bile after administration of AY4166, a novel D-phenylalanine-derivative hypoglycemic agent. [Erratum to document cited in CA126:325]
Takesada, Hiroko: Matsuda, Keizo: Ontrake, Ryoko; Mihara, Ryvichi: Ono, Ichiro; Tanaka, Kenzo; Naito, Masaki; Yatagai, Masanobu; Suzuki, Ei-Ichiro Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, 210, Japan
Bioorganic & Medicinal Chemistry (1997), 5(3), 637 CORPORATE SOURCE: AUTHOR(S):

searched 5/2/07 Page 61

SOURCE:

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

Journal UAGE:
UAGE:
Chapter 1771 (column 2, line 26) and 1772 (column 1, line 2), the functional group of M2 in Figure 1, which was converted from one of two methyl groups of AY4166, should read hydroxylmethyl instead of methoxyl. On page 1776, column 2, in the parentheses of the fourth line from last, 60 mg/kg should read 60 mg/man. CODEN: BMECEP; ISSN: 0968-0896 Elsevier DOCUMENT TYPE: PUBLISHER:

14 ANSWER 39 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1996:702133 HCAPLUS DOCUMENT NUMBER: 126:325

Structure determination of metabolites isolated from urine and bile after administration of A74166, a novel D-phenylalanine-derivative of hypoglycemic agent Takesada, Hicko: Matsuda, Keizo; Ohtake, Ryoko; Minara, Ryuichi; Ono, Ichiro; Tanaka, Kenzo; Naito, Masaki; Ztaqai, Masanobu; Suzuki, Ei-ichiro Central Research Laboratories, Ajinomoto Co., Inc., Kwasaki, 210, Japan
Bioorganic & Medicinal Chemistry (1996), 4(10), CORPORATE SOURCE:

AUTHOR(S):

CODEN: BMECEP; ISSN: 0968-0896

SOURCE:

Elsevier-English Journal DOCUMENT TYPE: LANGUAGE: PUBLISHER:

AB Mol. structures of 10 metabolites, which were isolated from urine (M1-M8) or bile (M9 and M10) after administration of AY4166 (N-(trans-4-isopropylyce)cheranecarbonyl)-D-phenylalaninho, with hypoglycentc activity, were elucidated by mass spectrometry and NMR. Four of these (M1, M2, M3 and M8) were hydroxyl derivs. of AY4166. Z (M9 and M10) were carboxylate derivs, via oxidation of R2 and M3, 3 (M4, M5 and M6) were glucuronic acid conjugates and the other (M7) was a dehydro derivative The structures for M1, M2, M3, M7, M8, M9 and M10 were confirmed by the coincidence of the retention time of MBC, and H1-NMR spectra between the isolated metabolites and authentic synthesized substances. For 3 glucuronic acid conjugates, M4, M5 and M6, structural confirmation was performed by a selective enzymic digestion with B-glucuronidase. M1 and M2/3 were about 5-6 and 3-fold less potent than AY4166, resp., and M7 was almost as potent as AY4166.

Preparation of trans-4-isopropylcyclohexanecarboxylic Matsuzawa, Toshihiro; Irie, Yasuo Ajinomoto KK, Japan Jpn. Kokai Tokkyo Koho, 3 pp. ANSWER 40 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ISION NUMBER: 1995:468819 HCAPLUS 123:55430 acid chloride PATENT ASSIGNEE(S): SOURCE: ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR (S):

Japanese FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE:

19930701 APPLICATION NO. JP 1993-163426 19950120 DATE KIND ø JP 07017899 PATENT NO.

JP 1993-163426 CASREACT 123:55430 PRIORITY APPLN. INFO.: OTHER SOURCE(S):

19930701

The title compound (I), useful as an intermediate for antidiabetic N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, is prepared by treatment of trans-4-isopropylcyclohexanecarboxylic acid (II) with P chloride. II was treated with PCl5 in 1,2-dichlorethane at 40° for 3 h to give 94% I and 0% the cis-isomer, whereas cis-isomer was

detected, when SOC12 was used instead of PC15.

L4 ANSWER 41 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1993:26,1002 HCAPLUS DOCUMENT NUMBER: 118:26,1002 Stable crystals of N-(+rang-4-

118:261002
Stable crystals of N-(trans-4isopropyl-gyclohexylcarbonyl)-D-phenylalanine
Sumkawa, Michito; Koguchi, Yoshihito; Ohgane, Takao;
Irie, Yasuo; Takahashi, Satoji
Ajinomoto Co., Inc., Japan
CODEN: EPXXDM INVENTOR (S):

PATENT ASSIGNEE(S):

English Patent LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE:

APPLICATION NO. KIND PATENT NO.

DATE -----19920729 19920729 19940201 A 19910730 A 19910808 19920729 19920729 AT 1992-306895 ES 1992-306895 CA 1994-2114678 LI, LU, NL, SE JP 1992-202686 JP 1991-189696 JP 1991-199453 EP 1992-306895 II, FR, GB, 19930820 19960619 19970315 19970616 19950802 19990427 19930203 19930505 19970305 A2 A3 B1 B1 DK, ES, A 1 B2 1 T 1 T 1 T 3 C 1 DE, R: AT, CH, D JP 05208943 JP 2508949 AT 149483 ES 2100291 CA 2114678 CA 2114678 PRIORITY APPLN. INFO.: EP 526171 EP 526171 EP 526171

Stable H-type crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I) are obtained by treating I with a solvent, at 5.0°. A solution of 5 g I in 20 mL acetone was added to a stirred mixture of 40 mL acetone and 60 mL water, at 25° to precipitate H-type crystals. The crystals have different m.p., IR spectrum and x-ray diffraction patterns from known forms of I and are not converted to other forms when ground, ΑB

L4 ANSWER 42 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:
10.15.58350 HCAPLUS
DOCUMENT NUMBER:
11.56362
TITLE:
N-(Cyclohexylcarbonyl)-D-phenylalanines and related compounds. A new class of oral hypoglycemic agents.

Shinkai, Hisashi; Nishikawa, Masahiko; Sato, Yusuke; Toi, Koji; Kumashiro, Izumi; Seto, Yoshiko; Fukuma, Mariko; Dan, Katsuaki; Toyoshima, Shigashi Cent. Res. Lab., Ajinomoto Co., Inc., Kawasaki, 210, CORPORATE SOURCE:

AUTHOR (S):

Journal of Medicinal Chemistry (1989), 32(7), 1436-41 CODEN: JMCMAR; ISSN: 0022-2623

searched 5/2/07 Page 63

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

LANGUAGE: OTHER SOURCE(S): DOCUMENT TYPE:

English CASREACT 111:58305

■ CO-D-Phe-OH

н

A series of analogs, e.g., I (R = alkyl, Ph), of N-(cyclohexylcarbonyl)-D-phenylalanine have been synthesized and evaluated for their hypoglycemic activity. Relationships were studied between the activity and the three-dimensional structure of the acyl moiety, which was characterized by high-resolution IH NMR spectroscopy and MNDO calcns. The role of the carboxyl group of the phenylalanine moiety was also studied by comparing the activities of the enantiomers, the decarboxyl derivative, the esters, and the amides of the phenylalanine derive. Thus, the structural requirements for possessing hypoglycemic activity was elucidated and a highly active compound, N-[(trans-4:sopropylcyclohexyl)carbonyl]-D-phenylalanine (I, R = GRMA2) was obtained, which showed a 20% blood glucose decrease at an oral dose of 1.6 mg/kg in fasted normal mice. ΑB

ANSWER 43 OF 44 HCAPLUS COPYRIGHT 2007 ACS ON STN SION NUMBER: 1987:85057 HCAPLUS L4 ANSWER 43 OF ACCESSION NUMBER:

Preparation of D-phenylalanine derivatives and their use as hypoglycemic agents
Toyoshima, Shigeshi; Seto, Yoshiko; Shinkai, Hisashi; Toyoshima, Kumashiro, Izumi
Ajinomoto Co., Inc., Japan
Eur. Pat. Appl., 25 pp. Correction of: 1987:19047 106:85057 Correction of: 106:19047 DOCUMENT NUMBER: TITLE:

PATENT ASSIGNEE(S): SOURCE:

INVENTOR(S):

English DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

| PA      | PATENT NO.     |       |    | KIND | DATE     | APE | APPLICATION NO. |    | DATE          |  |
|---------|----------------|-------|----|------|----------|-----|-----------------|----|---------------|--|
| :       |                |       |    |      |          | 1   |                 | :  | 1 1 1 1 1 1 1 |  |
| ΕP      | EP 196222      |       |    | A2   | 19861001 | EP  | EP 1986-302217  |    | 19860326      |  |
| EP      | 196222         |       |    | A3   | 19880224 |     |                 |    |               |  |
| EP      | 196222         |       |    | B1   | 19920129 |     |                 |    |               |  |
|         | R: CH,         | DE,   | F, |      | I.       |     |                 |    |               |  |
| J.      | 63054321       |       |    | ø    | 19880308 | ą,  | JP 1986-61833   |    | 19860319      |  |
| JP      | 04015221       |       |    | В    | 19920317 |     |                 |    |               |  |
| ns      | 4816484        |       |    | ď    | 19890328 | nS  | 1988-146719     |    | 19880121      |  |
| US      | 34878          |       |    | ഥ    | 19950314 | ns  | 1993-157564     |    | 19931123      |  |
| RIORITY | RIORITY APPLN. | INFO. | :  |      |          | J.P | 1985-62276      | Ą  | 19850327      |  |
|         |                |       |    |      |          | дĎ  | 1986-38111      | A1 | 19860222      |  |
|         |                |       |    |      |          | ns  | US 1986-844970  | A3 | 19860327      |  |
|         |                |       |    |      |          | SD  | 1988-146719     | A5 | 19880121      |  |
|         |                |       |    |      |          | SD  | 1989-844970     | B3 | 19890327      |  |

OTHER SOURCE(S): CASREACT 106:85057; MARRAT 106:85057
AB D-Phenylalanine derivs. D-R2CONR3CH(CO2R1)CH2Ph [I; R1 = H, C1-5 alkyl,

C6-12 aryl or aralkyl, Q, CH2CO2R3, CHMeOCOR3, CH2OCOCMe3; R2 = (un)substituted C6-12 aryl, 5- or 6-membered heterocyclyl, cycloalkyl, cycloalkeyl; R3 = H, C1-5 alkyl), their salts. and precursors which can be converted thereto in the human or animal body, useful as hypodyycemics, were prepared via conventional N-acylating reactions. D-Phenylalanine in 10% aqueous NaOH was successively treated with Me2CO, 4-Etc6H4COCl in Me2CO, and 10% aqueous NaOH to give 3% acylphenylanine D-II. At 25 mg/kg in mice, D-II decreased blood glucose 34% in min.

L4 ANSWER 44 OF 44 HCAPLUS COPPRIGHT 2007 ACS on STN
CCCSSION NUMBER: 1987:19047 HCAPLUS
DOCUMENT NUMBER: 106:19047
TITLE: 106:19047
TITLE: 17TAE: 17

EATENT NO. KIND DATE APPLICATION NO. DATE

EP 196222 A2

R: CH, DE, FR, GB, LI

PRIORITY APPLIN. INFO::

GI

o o et

Et CONHCHCPPh III

AB D-Phenylalanine derivs. D-RZCONR3CH(COZRI)CH2Ph [1; R1 = H, C1-5 alkyl, C6-12 aryl or aralkyl, Q, CH2CO2R3, CHMGOCOR3, CH2COCCM63; R2 = (un)substituted C6-12 aryl, 5- or 6-membered heterocyclyl, cycloalkyl, cycloalkenyl; R3 = H, C1-5 alkyl], their salts, and precursors which be converted thereto in the human or animal body, useful as hypoglycemics, were prepared via conventional N-acylating reactions. D-Phenylalanine in 10% aqueous NaOH was successively treated with Me2CO, and 10% aqueous NaOH was successively Exerted with Me2CO, and 10% aqueous NaOH was successively and all Necolating to a successively and the successively benefit and the successively and the successively and the successively of the successively and the successively benefit and the successively are successively and the successively and the successively and the successively are successively and the successively and the successively and the successively are successively and the successive and the successi

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SINCE FILE TOTAL

Page 65 searched 5/2/07

10/507255 SALTS OF NATEGLINIDE -str\_regno\_text -Search

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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION. LAST RELOADED: Apr 27, 2007 (20070427/UP).

Page 66 searched 5/2/07

chain nodes:

1 2 3 4 17 18 19 20 21 22 23 28

ring nodes:

5 6 7 8 9 10 11 12 13 14 15 16

chain bonds:

1-2 1-9 1-17 2-3 3-4 3-19 4-18 4-23 6-20 12-19 20-21 20-22 23-28

ring bonds:

5-6 5-10 6-7 7-8 8-9 9-10 11-12 11-16 12-13 13-14 14-15 15-16

exact/norm bonds:

1-2 1-17 2-3 4-18 4-23 5-6 5-10 6-7 7-8 8-9 9-10 23-28

exact bonds:

1-9 3-4 3-19 6-20 12-19 20-21 20-22

normalized bonds:

11-12 11-16 12-13 13-14 14-15 15-16

### G1:A,H,Ca,K,Mg,Na

### Match level:

1:CLASS2:CLASS3:CLASS4:CLASS5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS18:CLASS19:CLASS20:CLASS21:CLASS22:CLASS 23:CLASS28:CLASS

### Stereo Bonds:

9-1 (Single Wedge). 20-6 (Single Hash).

### Stereo Chiral Centers:

- (Parity=Even) (Parity=Odd) 6

### Stereo RSS Sets:

Type=Relative (Default). 2 Nodes= 6 9

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SINCE FILE ENTRY 0.21

FULL ESTIMATED COST

TOTAL SESSION 0.21

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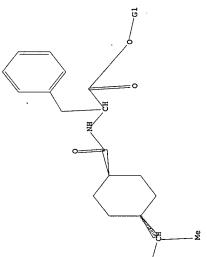
http://www.cas.org/support/stngen/stndoc/properties.html

=> Uploading C:\Program Files\Stnexp\Queries\2007 cases\10507255\nateglinide salt.str

=> d ll L1 HAS NO ANSWERS L1 STR

STRUCTURE UPLOADED Ξ

10/507255 SALTS OF NATEGLINIDE - STR salt Search



G1 A, H, Ca, K, Mg, Na

Structure attributes must be viewed using STN Express query preparation.

=> s 11 sss sam SAMPLE SEARCH INITIATED 18:29:42 FILE 'REGISTRY' SAMPLE SCREEN SEARCH COMPLETED - 603 TO ITERATE

603 ITERATIONS 100.0% PROCESSED SEARCH TIME: 00.00.01

5 ANSWERS

13533 ONLINE \*\*COMPLETE\*\*
BATCH \*\*COMPLETE\*\*
10587 TO 13533 FULL FILE PROJECTIONS: PROJECTED ITERATIONS: PROJECTED ANSWERS:

5 SEA SSS SAM L1

=> \$11 sss full FULL SEARCH INITIATED 18:29:47 FILE 'REGISTRY' FULL SCREEN SEARCH COMPLETED - 11826 TO ITERATE

100.0% PROCESSED 11826 ITERATIONS SEARCH TIME: 00.00.01

101 ANSWERS

101 SEA SSS FUL L1

=> fil hcaplu COST IN U.S. DOLLARS

TOTAL SESSION 172.31 SINCE FILE ENTRY 172.10 FULL ESTIMATED COST

FILE 'HCAPLUS' ENTERED AT 18:29:57 ON 02 MAY 2007

searched 5/2/07 Page 2

searched 5/2/07

Page 1

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46 L3/P => s 13/p

L4

=> d 14 1-46 hitstr

- ANSWER 1 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN LT LT
- 105816-04-4P, Nateglinide
  RL: IMF (Fundustrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
  (H type crystal, preparation of H type nateglinide crystal)
- 5 105816-04-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) S S

Absolute stereochemistry.

- COPYRIGHT 2007 ACS on STN ANSWER 2 OF 46 HCAPLUS 917394~14-0P L4 IT
- RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
  (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
  - (preparation of L-threonine derivs. with high therapeutic index) 917394-14-0 HCAPLUS
    L-Threonine, O-(N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-D-phenylalanyl]- (CA INDEX NAME)
    - ₹ ₹
- searched 5/2/07 Page 3

10/507255 SALTS OF NATEGLINIDE - STR salt Search

Absolute stereochemistry.

7 1

ANSWER 3 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-48, Nateglinide RE: IMF (Industrial manufacture); PRP (Properties); SFN (Synthetic preparation); PREP (Preparation)

(process for preparation of nateglinide, preferably in B-form) 105816-04-4 HCAPUUS 105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-

õ

INDEX NAME) Z Z

Absolute stereochemistry.

- 14
- ANSWER 4 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
  105816-04-4P, Nateglinide 105816-05-5P, L-Nateglinide
  RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL
  (Blological study); PREP (Preparation); USES (Uses)
  (direct separation and enantiosepn. of nateglinide stereoisomers by HPLC)
  - হ 105816-04-4 HCAPIUS D-Phenylalanine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-INDEX NAME) S S

Absolute stereochemistry.

L-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) HCAPLUS 105816-05-5 Z Z

Absolute stereochemistry

17

ANSWER 5 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 594837-85-1P RI: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(in a one-pot process for the preparation of nateglinide)
59487-85-1 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
monosodium salt (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

● Na

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (one-pot process for the preparation of nateglinide) 105816-04-4 HCAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA INDEX NAME) 105816-04-4P, Nateglinide II

C Z

Absolute stereochemistry

L4 II

ANSWER 6 OF 46 HCAPIUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

searched 5/2/07 Page 5

10/507255 SALTS OF NATEGLINIDE - STR salt Search

₹ 3

(crystallization of nateglinide as form B)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA
INDEX NAME)

Absolute stereochemistry.

L4 IT

ANSWER 7 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 594837-89-5P RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (process for the preparation of polymorphic crystalline forms of nateglinide

Z Z

ammonium salt)
84837-89-5 HCAPLUS
D-Phenylalanine, N-[[trans-4-(l-methylethyl)cyclohexyl]carbonyl]-, ammonium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry

• x NH3

L4 IT

ANSWER 8 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 909102-82-5P 909102-83-6P 909102-84-7P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PRE (Preparation) (preparation of fluoro-N-[(isopropyl)cyclohexyl]carbonyl]-D-phenylalanine derivs. (nateglinide analogs) and study of their activity as

hypoglycemic agents)
909102-82-55 HCARDINS
D-Phenylalanine, 4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl], hydrochloride, (9CI) (CA INDEX NAME) **Z** 33

Absolute stereochemistry. Rotation (-).

● HC1

D-Phenylalanine, 3-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrochloride (9CI) (CA INDEX NAME) 909102-83-6 HCAPLUS S S

Absolute stereochemistry. Rotation (-).

● HC1

909102-84-7 HCAPLUS
D-Phenylalanine, 2-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl], hydrochloride (9CI) (CA INDEX NAME) S S

Absolute stereochemistry. Rotation (-).

• HC1

909102-79-0P, 4-Fluoro-N-[[trans-4-(1-methylethy])cyclohexy]carbonyl]-L-phenylalanine monohydrochloride 909102-80-3P 909102-81-4P 809102-81-4P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) Ħ

searched 5/2/07 Page 7

10/507255 SALTS OF NATEGLINIDE - STR salt Search

(preparation of fluoro-N-[[(isopropyl)cyclohexyl]carbonyl]-L-phenylalanine
derivs. (nateglinide analogs) and study of their activity as
hypodytycanic agents)
909102-79-0 HCAPLUS
L-Phenylalanine, 4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl], hydrochloride (9CI) (CA INDEX NAME)

S S

Absolute stereochemistry. Rotation (+).

● HC1

909102-80-3 HCAPLUS
L-Phenylalanine, 3-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl], hydrochloride (9CI) (CA INDEX NAME) S S

Absolute stereochemistry. Rotation (+).

909102-81-4 HCAPLUS L-Phenylalanine, 2-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrochloride (9CI) (CA INDEX NAME) S S

Absolute stereochemistry. Rotation (+).

ANSWER 9 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 14

105816-04-4P RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of nateglinide via acylation of phenylalanine with isopropylcyclohexanecarbonyl chloride in a mixture of dioxane or THF and

105816-04-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME)

Absolute stereochemistry

Z Z

15

ANSWER 10 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP

(preparation of nateglinide via acylation of phenylalanine with isopropylcyclohexanecarbonyl chloride in a mixture of DMF and H2O) 105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA

Z Z

Absolute stereochemistry.

searched 5/2/07 Page 9

10/507255 SALTS OF NATEGLINIDE - STR salt Search

I T

ANSWER 11 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: PRP (Properties); SFN (Synthetic preparation); PREP (Preparation) for (process for the preparation of the crystalline B-form nateglinide from D-phenylalanine Me ester) 105816-04-4 HCAPLUS 105816-04-4 HCAPLUS 10-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA INDEX NAME)

S S

Absolute stereochemistry.

COPYRIGHT 2007 ACS on STN ANSWER 12 OF 46 HCA 183996-89-6P 727985-727985-70-8P 727985-L4 IT

727985-70-8P 727985-71-9P 727985-72-0P 727985-73-1P 727985-74-2P 727985-73-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES 727985-85-5P

S (preparation of alanine derivs. as antidiabetics)
183996-89-6 HCAPLUS
D-Yycosine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
INDEX NAME) Z Z

Absolute stereochemistry

727985-68-4 HCAPLUS L-Tyrosine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-0-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9Cl) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (+)

127985-69-5 HCAPLUS
D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-0-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (-).

727985-70-8 HCAPLUS
L-Tyrosine, O-[2-(2-benzoxazolylmethylamino)ethyl]-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (+).

727985-71-9 HCAPLUS
D-Tyrosine, O-[2-(2-benzoxazolylmethylamino)ethyl]-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) **2** 2

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

727985-72-0 HCAPLUS
L-Tyrosine, O-[2-(1H-indol-1-yl)ethyl]-N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

727985-73-1 HCAPLUS
D-Tyrosine, O-[2-(1H-indol-1-yl)ethyl]-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9Cl) (CA INDEX NAME) S S

Absolute stereochemistry.

727985-74-2 HCAPLUS
L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[[4-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME) ₹8

Absolute stereochemistry. Rotation (+).

727985-75-3 HCAPLUS
D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[[4-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

727985-76-4 HCAPLUS
L-Tyrosine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-O-(phenylmethyl)- (9CI) (CA INDEX NAME) S &

Absolute stereochemistry. Rotation (+).

Z Z

727985-77-5 HCAPLUS
D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

727985-78-6 HCAPLUS
L-Tyrosine, O-butyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 727985-79-7 HCAPLUS
CN D-Tyrosine, O-butyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

727985-80-0 HCAPLUS L-Tyrosine, O-ethyl-N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 727985-81-1 HCAPLUS

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CN D-Tyrosine, O-ethyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

727985-82-2 HCAPLUS L-Tyrosine, O-methyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME) S S

Absolute stereochemistry. Rotation (+).

Z Z

127985-83-3 HCAPLUS
D-Tyrosine, O-methyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

S S

727985-84-4 #CAPLUS L-Tyrosine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) INDEX NAME)

Absolute stereochemistry. Rotation (+).

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

727985-85-5 HCAPLUS
L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-0-[2-(methyl-2-pyridinylamino)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT 727985-89-9P 727985-92-4P 727985-93-5P H

(Reactant or reagent)
(preparation of alanine derivs. as antidiabetics)
(2798-89-9 HCAPLUS
L-Tyrosine, N-[(trans-4-(1-methylethyl)cyclohexy]]carbonyl]-0-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]-, methyl ester (9CI) (CA INDEX NAME) S S

Absolute stereochemistry.

727985-92-4 HCAPLUS
L-Tyrosine, O-[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]ethyl]-N[[trans-4-[1-methylethyl]cyclohexyl]carbonyl]-, methyl ester (9CI) (CA
INDEX NAME) Z Z

727985-93-5 HCAPLUS L-Tyrosine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-O-[2-(methyl-2-pyridinylamino)ethyl]-, methyl ester (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

727985-87-7P 727985-88-8P RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (USes) H

(preparation of alamine derivs. as antidiabetics)
727985-87-7 HCAPLUS
1-Typosine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME) ₹ ₹

Absolute stereochemistry.

₹ ₹

727985-88-8 HCAPLUS D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

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727985-86-6P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of alanine derivs. as antidiabetics)
727985-66-6 ENCARUS.
D-Tyzosine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-0-[2-(methyl-2-pyridinylamino)ethyl]- (9CI) (CA INDEX NAME)

₹ 5

Absolute stereochemistry. Rotation (-).

L4 IT

ANSWER 13 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 187728-85-4P RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP

(Preparation); RACT (Reactant or reagent)
(targeted pancreatic B-cell imaging and therapy)
187728-85-4 HCAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME) S. 25

Absolute stereochemistry

ANSWER 14 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4DP, Nateglinide, analogs 851863-95-1P 851863-97-3P 851863-97-8 14

851864-03-4P 851864-05-6P 851864-07-8P 851864-09-0P 851864-11-4P 851864-13-6P 851864-11-4P 851864-13-6P 851864-13-4P 851864-13-4P 851864-19-2P 851864-27-4P 851864-27-4P 851864-27-4P 851864-27-4P 851864-27-4P 851864-27-4P 851864-27-4P 851864-27-4P 851864-37-4P 85186

S (syntheses and hypoglycenia activities of N-(trans-4-isopro-pylcyclohexylcarbonyl)-P-ring substituted phenylalanines):
105816-04-4 HGARIUS
1-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) Z Z

Absolute stereochemistry.

D-Phenylalanine, N-[[trans-4-(l-methylethyl)cyclohexyl]carbonyl]-3-nitro-(9CI) (CA INDEX NAME) 851863-95-1 HCAPLUS Z Z

Absolute stereochemistry. Rotation (-).

L-Phenylalanine, N-[[trans-4-(l-methylethyl)cyclohexyl]carbonyl]-3-nitro-(9C1) (CA INDEX NAME) 851863-97-3 HCAPLUS Z Z

Absolute stereochemistry. Rotation (+).

æ 8

851863-99-5 HCAPLUS D-Phenylalanine, 2-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-

searched 5/2/07 Page 19

10/507255 SALTS OF NATEGLINIDE - STR salt Search

(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-)

851864-01-2 HCAPLUS L-Phenylalanine, 2-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

851864-03-4 HCAPLUS D-Phenylalanine, 3-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (-).

851864-05-6 HCAPLUS L-Phenylalanine, 3-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

Absolute stereochemistry. Rotation (-).

L-Phenylalanine, 4-chloro-N-[[trans-4-(l-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME) RN 851864-09-0 HCAPLUS CN L-Phenylalanine 4-ch

Absolute stereochemistry. Rotation (+).

851864-11-4 HCAPLUS
D-Phenylalanine, 4-bromo-N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

RN 851864-13-6 HCAPLUS

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

CN L-Phenylalanine, 4-bromo-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9Cl) (CR INDEX NAME)

Absolute stereochemistry.

RN 851864-15-8 HCAPLUS
CN D-Phenylalanine, 2-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9C1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 851864-17-0 HCAPLUS
CN L-Phenylalanine, 2-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9C1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

851864-19-2 HCAPLUS
D-Phenylalanine, 3-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

C &

851864-21-6 HCAPLUS L-Phenylalanine, 3-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

851864-23-8 HCAPLUS D-Phenylalanine, 4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (-).

RN 851864-25-0 HCAPLUS
CN L-Phenylalanine, 4-fluoro-N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl}(9C1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 851864-27-2 HCAPLUS

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10/507255 SALIS OF NATEGLINIDE - STR salt Search

D-Phenylalanine, 3-chloro-4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9Cl) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

851864-29-4 HCAPLUS
L-Phenylalanine, 3-chloro-4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9Cl) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (+).

RN 851864-31-8 HCAPLUS
CN D-Phenylalanine, 3,4-dichloro-N-[[trans-4-(1-methylethyl]cyclohexyl]carbon
yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 851864-33-0 HCAPLUS
CN L-Phenylalanine, 3,4-dichloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbon
y1]- (9C1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

851864-35-2 HCAPLUS
D-Phenylalanine, 3-chloro-2-methyl-N-[{trans-4-(1-methylethyl}cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (-).

Z Z

851864-37-4 HCAPLUS
L-Phenylalanine, 3-chloro-2-methyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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851864-07-28 851884-09-0P 851864-11-4P 851864-13-6P 851884-16-8P 851864-11-0P 851864-29-2P 851864-23-8P 851864-23-8P 851864-29-4P 851864-31-8P 851864-33-0P 851864-35-2P 851864-37-4P 851864-33-0P 851864-35-3P 851864-35-4P 851864-37-4P 851864-3

(preparation of aromatic amino acid derivs. for treatment of blood sugar disorders)

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

851863-95-1 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-3-nitro(9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (-).

Absolute stereochemistry. Rotation (+).

851863-97-3 HCAPLUS L-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl]-3-nitro-(9CI) (CA INDEX NAME)

**₹**8

851863-99-5 HCAPLUS D-Phenylalanine, 2-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-)

851864-01-2 HCAPLUS L-Phenylalanine, 2-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 851864-03-4 HCAPLUS CN D-Phenylalanine, 3-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 851864-05-6 HCAPLUS
CN L-Phenylalanine, 3-chloro-N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 851864-07-8 HCAPLUS
CN D-Phenylalanine, 4-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 851864-09-0 HCAPLUS

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

CN L-Phenylalanine, 4-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 851864-11-4 HCAPLUS CN D-Phenylalanine, 4-bromo-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 851864-13-6 HCAPLUS
CN L-Phenylalanine, 4-bromo-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 851864-15-8 HCAPLUS
CN D-Phenylalanine, 2-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

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851864-17-0 HCAPLUS L-Phenylalanine, 2-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME) Z 3

Absolute stereochemistry. Rotation (+).

RN 851864-19-2 HCAPLUS
CN D-Phenylalanine, 3-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 851864-21-6 HCAPLUS
CN L-Phenylalanine, 3-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9C1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 851864-23-8 HCAPLUS

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

CN D-Phenylalanine, 4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 851864-25-0 HCAPLUS
CN L-Phenylalanine, 4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 851864-27-2 HCAPLUS
CN D-Phenylalanine, 3-chloro-4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

851864-29-4 HCAPLUS L-Phenylalanine, 3-chloro-4-fluoro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

851864-31-8 HCAPLUS
D-Phenylalanine, 3,4-dichloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbon yl]- (9CI) (CA INDEX NAME) S 25

Absolute stereochemistry. Rotation (-).

L-Phenylalanine, 3,4-dichloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbon yl]- (9C1) (CA INDEX NAME) 851864-33-0 HCAPLUS Z Z

Absolute stereochemistry. Rotation (+).

851864-35-2 HCAPLUS Z Z

D-Phenylalanine, 3-chloro-2-methyl-N-[[trans-4-(1-methylethyl) cyclohexyl]carbonyl]- (9Cl) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

S 53

851864-37-4 HCAPLUS L-Phenylalanine, 3-chloro-2-methyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4

ANSWER 16 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
105816-04-4P, Nateglinide
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP
(Physical process); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of crystalline form of nateglinide for dosage forms)
105816-04-4 HCAPLUS
INDEX NAME)

S S

Absolute stereochemistry.

L4 IT

ANSWER 17 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-40, Mateglinide (Synthetic preparation); PREP (Proparation) RI: PRP (Properties); SPN (Synthetic preparation); RREP (Preparation) (saponification and neutralization process for the preparation of chirally

pure

nateglinide from its lower alkyl esters and nateglinide polymorphic crystalline modifications)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA Z Z

Absolute stereochemistry.

ANSWER 18 OF 46 HCAPIUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP 114

(large scale synthesis of nateglinide)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) Z 2

Absolute stereochemistry.

COPYRIGHT 2007 ACS on STN 727985-69-5P ANSWER 19 OF 46 HCAPLUS COPYRIGHT 2007 183996-89-6P 727985-69-5P 727985-71-9P 727985-70-9P 727985-73-1P 727985-77-5P 727985-73-1P 727985-74-2P 727985-78-6P 727985-78-6P 727985-78-6P 727985-78-7P 727985-78-6P 727985-78-7P 727985-81-1P 727985-82-2P 727985-83-3P 727985-81-1P 고다

727985-85-5P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) INDEX NAME) (preparation of alanine compds. as antidiabetics) 183996-89-6 HCAPLUS S S

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

727985-68-4 HCAPLUS L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl}- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+)

727985-69-5 HCAPLUS
D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (GA INDEX NAME) S S

Absolute stereochemistry. Rotation (-).

727985-70-8 HCAPLUS

L-Tyrosine, O-[2-(2-benzoxazolylmethylamino)ethyl]-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9Cl) (CA INDEX NAME) S 53

Absolute stereochemistry. Rotation (+).

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D-Tyrosine, O-[2-(2-benzoxazolylmethylamino)ethyl}-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) 727985-71-9 HCAPLUS S S

Absolute stereochemistry.

727985-72-0 HCAPLUS L-Tyrosine, O-{2-(1H-indol-1-yl)ethyl}-N-{[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) ₹ S

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

727985-73-1 HCAPLUS
D-Tyrosine, O-[2-(1H-indol-1-yl)ethyl]-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9Cl) (CA INDEX NAWE)

Absolute stereochemistry.

727985-74-2 HCAPLUS
L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[[4-(trifluoromethyl)phenyl]methyl]- (9Cl) (CA INDEX NAME) S S

Absolute stereochemistry. Rotation (+).

D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[[4-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME) 727985-75-3 HCAPLUS

Absolute stereochemistry.

727985-76-4 HCAPLUS
L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

727985-77-5 HCAPLUS
D-Tyrosine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-O-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 727985-78-6 HCAPLUS
CN L-Tyrosine, O-butyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 727985-79-7 HCAPLUS
CN D-Tyrosine, O-butyl-N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

727985-80-0 HCAPLUS
L-Tyrosine, O-ethyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 727985-81-1 HCAPLUS
CN D-Tyrosine, O-ethyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

RN 727985-82-2 HCAPLUS
CN L-Tyrosine, O-methyl-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl](9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

727985-83-3 HCAPLUS

D-Tyrosine, O-methyl.N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

<u>g</u> 727985-84-4 HCAPLUS L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) INDEX NAME) Z Z

Absolute stereochemistry. Rotation (+).

727985-85-5 HCAPLUS
L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-0-[2-(methyl-2-pyridinylamino)ethyl]- (9CI) (CA INDEX NAME) **₹**8

Absolute stereochemistry. Rotation (+).

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Absolute stereochemistry

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

Z Z

Absolute stereochemistry.

727985-93-5 HCAPLUS Z Z

L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[2-(methyl-2-pyridinylamino)ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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727985-87-7P 727985-88-8P RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); FACT (Reactant or reagent); USES (Uses)

(preparation of alanine compds. as antidiabetics)
727985-87-7 HGARUS
L-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, methyl ester
(9CI) (CA INDEX NAME) S S

Absolute stereochemistry.

727985-88-8 HCAPLUS D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME) S S

Absolute stereochemistry.

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of alanine compds. as antidiabetics) 727985-86-6 HCAPLUS 727985-86-6P

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D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-O-[2-(methyl-2-pyridinylamino)ethyl]- (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry. Rotation (-).

17

ANSWER 20 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide; TR (Bactant); SPN (Synthetic preparation); THU RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (process for the formation of a crystalline polymorphic form of nateglinide) 105816-04-4 HCAPLUS

<u>g</u> D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME)

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

Absolute stereochemistry.

ANSWER 21 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 669087-90-5P

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RI. PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Blological study); PREP (Preparation); USES (Uses) (pharmaceutical compns. containing nateglinide inclusion complexes with b-cyclodextrin and its derivs.) (69987-90-5 FGARLUS PRARLUS.) (PD-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with p-cyclodextrin (3:1) (9C1) (CA INDEX NAME)

Z Z

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CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

7 ਠੋ CRN 7585-39-9 CMF C42 H70 035

Absolute stereochemistry.

PAGE 2-A

105816-04-4DP, Nateglinide, complexes with hydroxypropyl B-cyclodextrin 669087-91-6P 669087-92-7P 669087-93-8P 669087-94-9P 669087-95-0P II

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pharmaceutical compus. containing nateglinide inclusion complexes with B-cyclodextrin and its derivs.)
105815-04-4 HGAPLUS
10-Phenylalanine, N-{(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (GA INDEX NAME) Z 2

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

669087-91-6 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl}-, compd.with P-cyclodextrin (2:1) (9CI) (CA INDEX NAME) ≅ S

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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CRN 7585-39-9 CMF C42 H70 035

Absolute stereochemistry.

PAGE 1-A

PAGE 2-A

RN 669087-92-7 HCAPLUS
CN D-Phenylalanine, "-|[trans-4-(1-methylethyl)|cyclohexyl]|carbonyl]-, compd.
with 2A, 2B, 2C, 2D, 2E, 2F, 2G, 6B, 6E, 6E, 6E, 6F, 6G-tetradeca-O-methyl- \(\theta\)- cyclodextrin (1:1) (9C1) (CA INDEX NAME)

CM 11

CRN 105816-04-4 CMF C19 H27 N O3 Absolute stereochemistry.

CM CM CRN 51166-71-3 CMF C56 H98 035 Absolute stereochemistry.

10/507255 SALTS OF NATEGLINIDE - STR salt Search

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PAGE 2-A

RN 669087-93-8 HCAPLUS
CN P-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, com with 2A, 2B, 2C, 2D, 2E, 2E, 2G, 3B, 3B, 3C, 3D, 3E, 3E, 3G, 6B, 6E, 6E, 6E, 6E, 6E- heneicosa-O-methyl-β-cyclodextrin (1:1) (9CI) (CA INDEX NAME)

GM 1

CRN 105816-04-4 CMF C19 H27 N 03 Absolute stereochemistry.

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CRN 55216-11-0 CMF C63 H112 035

Absolute stereochemistry.

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PAGE 2-A

669087-94-9 HCAPLUS Phenylalanine, W-[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 2A,2B,2C,2D,2E,2E,2E,6A,6B,6C,6D,6E,6F,6G-tetradeca-O-ethyl- \bar{\rho}-cyclodextrin (1:1) (9C1) (CA INDEX NAME) S S

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CRN 111689-03-3 CMF C70 H126 O35

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

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CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

669087-95-0 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-, compd. with P-cyclodextrin (1:1) (9CI) (CA INDEX NAME) **≅** ₹

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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CRN 7585-39-9 CMF C42 H70 O35

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

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669088-00-0 HCAPLUS
Phenylalanine, W-[[Lrans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with 2A,2B,2C,2D,2E,2E,2G,3A,3B,3C,3D,3E,3E,6B,6B,6C,6D,6E,6F,6G-heneicosa-O-ethyl-p-cyclodextrin (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 111689-01-1 CMF C84 H154 035

Absolute stereochemistry.

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PAGE 2-A

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CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

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ANSWER 22 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
105816-04-4P, Nateglinide
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN
(Synthetic preparation); PREP (Preparation)
(Synthesis and purification of nateglinide)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CAINDEX NAME)

Z Z

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Absolute stereochemistry.

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ANSWER 23 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
105816-04-4P, Nateglinide

Lis FEP (Physical, engineering or chemical process); PYP (Physical process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)

[Preparation of polymorphic forms of nateglinide)
105816-04-4 HCAPLUS
Phenylalanine, N-[(trans-4-(1-methylethyl);cyclohexyl]carbonyl]- (CA

INDEX NAME) £ 5.

Absolute stereochemistry.

polymorphs 651353-42-3P 631353-43-4P 651353-44-5P 651353-45-6P 651353-46-9P 651353-44-9P 651353-47-8P 651353-51-3P 651353-51-4P 651353-52-5P 651353-52-5P 651353-53-6P 105816-04-4DP, Nateglinide, H

RL: PEP (Physical, engineering or chemical process); PYP (Physical

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREC (Process); USES (Uses) (preparation of polymorphic forms of nateglinide)
108816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME)

Z Z

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Absolute stereochemistry.

651353-42-3 HCAPLUS D-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl}-, compd.with methanol (9CI) (CA INDEX NAME) Z Z

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CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry

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67-56-1 C H4 O CRN OMF

H3C-OH

651353-43-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with ethanol (9C1) (CA INDEX NAME) Z Z

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105816-04-4 C19 H27 N O3 CRN CMF

Absolute stereochemistry.

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CRN 64-17-5 CMF C2 H6 O

н3С-сн5-он

651353-44-5 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with 1-butanol (9CI) (CA INDEX NAME) Z Z

CM 1

CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

₹

CRN 71-36-3 CMF C4 H10 O

Н3С- СН2-СН2-СН2-ОН

651353-45-6 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with 1-propanol (9CI) (CA INDEX NAME) Z Z

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

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CRN 71-23-8 CMF C3 H8 O

Н3С-СН2-СН2-ОН

651353-46-7 HCAPLUS
D-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl}carbonyl}-, compd.with N,N-dimethylacetamide (9CI) (CA INDEX NAME) Z Z

CM 1

CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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CRN 127-19-5 CMF C4 H9 N O

Me-N-Ac

651353-47-8 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-methyl-2-pyrrolidinone (9CI) (CA INDEX NAME) **3** 33

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CRN 105816-04-4

CMF C19 H27 N O3

Absolute stereochemistry.

CM 2

CRN 872-50-4 CMF C5 H9 N O

651353-48-9 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.with N,N-dimethylformamide (9CI) (CA INDEX NAME) S S

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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CRN 68-12-2 CMF C3 H7 N O

H3C- N- CH-0 CH3

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

651353-49-0 HCAPLUS
D-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with 1,2-dimethoxyethane (9CI) (CA INDEX NAME) S 53

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

~ ₹ CRN 110-71-4 CMF C4 H10 O2

MeO-CH2-CH2-OMe

651353-50-3 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with.dimethylbenzene (9CI) (CA INDEX NAME) Z Z

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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CRN 1330-20-7 CMF C8 H10 CCI IDS

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651353-51-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl}-, compd.
with tetrachloromethane (9CI) (CA INDEX NAME) Z 3

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

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CRN 56-23-5 CMF C C14

651353-52-5 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl}-, compd.
with 1,2-dichloroethane (9CI) (CA INDEX NAME) ₹ S

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

searched 5/2/07 Page 57

10/507255 SALTS OF NATEGLINIDE - STR salt Search

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CRN 107-06-2 CMF C2 H4 C12

C1-CH2-CH2-C1

651353-53-6 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-, compd.
with trichloromethane (9CI) (CA INDEX NAME) Z 3

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CRN 105816-04-4 CMF C19 H27 N 03

Absolute stereochemistry.

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CRN 67-66-3 CMF C H Cl3

C1-CH-C1

651353-54-7 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with heptane (9CI) (CA INDEX NAME) Z 3

₹

CMF C19 H27 N O3

Absolute stereochemistry.

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142-82-5 C7 H16 CRN

Me- (CH2) 5- Me

ANSWER 24 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP L4

S S

(process for preparation of nateglinide)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA

Absolute stereochemistry.

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ANSWER 25 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PREP (Preparation); PROC (Process)

(process for the preparation of a crystal polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide)) 105816-04-4 HCAPLUS

D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) S S

Absolute stereochemistry.

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

L4 ANSWER 26 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
IT 105816-04-4P, Nateglinide
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of A, M, and P type nateglinide crystals by crystallization from mixture

of solvents) 105816-04-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) ₹ 5

Absolute stereochemistry.

ANSWER 27 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 592523-1-4P 592523-32-5P 59254-24-8P 594837-85-1P 594837-87-3P 17

RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation) (preparation and properties of nateglinide salts) 59253-31-4 HcAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.with 1-deoxy-1-(methylamino)-D-glucitol (1:1) (9CI) (CA INDEX NAME) S S

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CRN 105816-04-4 CMF C19 H27 N O3

Absolute stereochemistry.

CM 2

CRN 6284-40-8 CMF C7 H17 N O5 Absolute stereochemistry.

RN 592523-32-5 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (9CI) (CA INDEX NAME)

CM 1 CRN 105816-04-4 CMF C19 H27 N 03 Absolute stereochemistry.

CM 2

CRN 77-86-1 CMF C4 H11 N 03

ипно-си2-с-си2-он си2-он RN 592524-24-8 HCAPIUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.
with L-lysine (1:1) (9CI) (CA INDEX NAME)

7

CMF C19 H27 N O3

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10/507255 SALTS OF NATEGLINIDE - STR salt Search

Absolute stereochemistry.

CM 2

CRN 56-87-1 CMF C6 H14 N2 O2 Absolute stereochemistry.

C S (CH2) 4 NH2

RN 594837-85-1 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Na

RN 594837-86-2 HCAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
monopotassium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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594837-87-3 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, calcium salt (2:1) (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

●1/2 Ca

594837-89-5 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, ammonium salt (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry

• x NH3

- ANSWER 28 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
  105816-04-4P, Nateglinide
  RL: PNU (Preparation, unclassified); PREP (Preparation)
  (preparation of)
  105816-04-4 HCAPLUS
  D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-L4 IT
- Z Z

searched 5/2/07 Page 63

10/507255 SALTS OF NATEGLINIDE - STR salt Search

INDEX NAME)

Absolute stereochemistry.

14

ANSWER 29 OF 46. HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide RL: FWI (Preparation, unclassified); PREP (Preparation) (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide) 105816-04-4 HCAPLUS 105816-04-4 HCAPLUS ID-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) Z Z

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Absolute stereochemistry.

ANSWER 30 OF 46 HCAPLUS COPYRIGHT 2007 ACS ON STN 105816-04-4P L4 IT

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);
PUR (Purification or recovery); ANST (Analytical study); BIOL (Biological
study); PREP (Preparation)

S S (separation of cis-isomer of nateglinide by HPLC method)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]INDEX NAME) Z Z

Absolute stereochemistry.

ANSWER 31 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (Synthesis of nateglinide as antidiabetic drug) 105816-04-4 RCAPLUS D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA INDEX NAME)

Z Z

Absolute stereochemistry

ANSWER 32 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P, Nateglinide 7 T

RL: PAC (Pharmacológical activity); PUR (Purification or recovery); ? (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

THU

(industrial process for producing B-form nateglinide crystals) 105816-04-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) Z Z

Absolute stereochemistry.

HCAPLUS COPYRIGHT 2007 ACS on STN ANSWER 33 OF 46 HCAPLUS 105816-04-4P, Nateglinide 17

RL: IMF (Industrial manufacture); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL fablogicial study); PREP (Preparation); USES (Uses) (process for producing nateglinide crystals)

S S

105816-04-4 HCAPLUS D-Phenylalanine, N-[{trans-4-(l-methylethyl)cyclohexyl]carbonyl]-INDEX NAME)

Absolute stereochemistry

searched 5/2/07 Page 65

10/507255 SALTS OF NATEGLINIDE - STR salt Search

ANSWER 34 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP L4 IT

(Preparation)

õ (process for preparation of acylphenylalanines)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-INDEX NAME) Z Z

Absolute stereochemistry.

L4

ANSWER 35 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 108916-04-404-04. Nateglinide, nitroxyl-containing derivs. MEL: PRC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(drug candidates; preparation of antidiabetic agents comprising antiinflammatory or analgesic drugs, selected bivalent linkers, and

nitrate esters) 105816-04-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA INDEX NAME) S S

Absolute stereochemistry.

17

ANSWER 36 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 475168-20-8P 475168-27-5P RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(stereoselective preparation of [14C]- and [3H]DJN608 [Starlix]) 475168-20-8 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl-14C]-, methyl ester (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

D-Phenylalanine, 4-chloro-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, phenylmethyl ester (9Cl) (CA INDEX NAME) 475168-27-5 HCAPLUS S 23

Absolute stereochemistry.

ij

475168-21-9P 475168-29-7P RL: SPN (Synthetic preparation); PREP (Preparation) (stereoselective preparation of [14C]- and [3H]DJN608 [Starlix]) 475168-21-9 HGAPLUS

D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl-14C]-(9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

475168-29-7 HCAPLUS
D-Phenylalanine-4-t, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-,
phenylmethyl ester (9CI) (CA INDEX NAME) Z Z

Absolute stereochemistry.

searched 5/2/07 Page 67

10/507255 SALTS OF NATEGLINIDE - STR salt Search

ANSWER 37 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
105816-04-4-DP, Natechinide, B crystal type
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent) (preparation and crystalline forms of)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]INDEX NAME) 14 Z Z

õ

Absolute stereochemistry.

SPN (Synthetic preparation); PREP (Preparation) (synthesis of Nateglinide RL: SPN

ANSWER 38 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (Preparation and effect of cycloalkylcarboxamide derivs as cysteine 17

(CA professe inhibitors)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-Z Z

Absolute stereochemistry.

HCAPLUS COPYRIGHT 2007 ACS on STN ANSWER 39 OF 46 321371-24-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); HW (Therapeutic use); BLOL (Biological study); PREP (Preparation); USES (Uses) (preparation of thiazolidinediones as insulinotropics and insulin

Z Z

321371-24-8 HCAPLUS
Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]-N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Relative stereochemistry.

321371-23-7P RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of thiazolidinediones as insulinotropics and insulin H

321371-23-7 HCAPLUS
Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Relative stereochemistry.

S S

L4 IT

ANSWER 40 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
18396-89-66
RL. BSU (Biological study, unclassified); MFM (Metabolic formation); SPN
(Synthetic preparation); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)
1813996-89-6 HCAPLUS

D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) Z Z

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Absolute stereochemistry

searched 5/2/07 Page 69

10/507255 SALTS OF NATEGLINIDE - STR salt Search

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(structure of metabolites of AY4166 as hypoglycemic (Erratum))
183997-01-5 HCAPLUS 183997-01-5P

D-Tyrosine, N-[[trans-4-(1-methylethyl]cyclohexyl]carbonyl]-, phenylmethyl ester (9CI) (CA INDEX NAME) æ 5

Absolute stereochemistry

ANSWER 41 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 183996-89-6P 17

RI. BSU (Bloogical study, unclassified); MFM (Metabolic formation); SPN (Synthetic preparation); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation) (structure of metabolites of AY4166 as hypoglycemic) 18396-89-6 (GARUUS D-Tyrosine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA

Z Z

Absolute stereochemistry

183997-01-5P
RL: RCT (Reactant); SPM (Synthetic preparation); PREP (Preparation); RACT (Reactant or respect)
(Reactant or respect)
(structure of metabolites of AY4166 as hypoglycemic)
183997-01-5 HCAPLUS Ľ Z

Absolute stereochemistry.

ANSWER 42 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 1.4 1.7

103816-04-4P RL: PNU (Preparation, unclassified); PREP (Preparation)

(preparation of trans-4-isopropylcyclohexanecarboxylic acid chloride as intermediate for antidiabetic agent by chlorination of the acid with P

105816-04-4 HCAPLUS D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-Z Z

Absolute stereochemistry.

ANSWER 43 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P RL: PREP (Preparation) 17

(crystals, stable, preparation of)
105816-04-4 HCAPLUS
D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-Z 2

5

Absolute stereochemistry

searched 5/2/07 Page 71

10/507255 SALTS OF NATEGLINIDE - STR salt Search

ANSWER 44 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P L4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (Dreparation and hypoglycemic activity of) [preparation and hypoglycemic activity of) D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA INDEX NAME)

Z Z

Absolute stereochemistry.

HCAPLUS COPYRIGHT 2007 ACS on STN ANSWER 45 OF 46 HCAPLUS 105816-04-4P 105816-05-5P 17

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as hypoglycemic)
108816-04-4 HCAPLUS
D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (CA INDEX NAME) Z Z

Absolute stereochemistry.

105816-05-5 HCAPLUS
L-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)
(CA INDEX NAME) Z Z

Absolute stereochemistry.

ANSWER 46 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 105816-04-4P 105816-05-5P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as hypoglycemic)
105816-04-4 HCAPIUS
D-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl]carbonyl]-

<u>5</u> INDEX NAME) S 53

Absolute stereochemistry.

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L-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME) 105816-05-5 HCAPLUS Z Z

Absolute stereochemistry.

=> d his

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FILE 'REGISTRY' ENTERED AT 18:29:05 ON 02 MAY 2007 STRUCTURE UPLOADED 5 LI SSS SAM 101 S.LI SSS FULL 222

FILE 'HCAPLUS' ENTERED AT 18:29:57 ON 02 MAY 2007 46 S 13/P 7

=> d 14 1-46 ibib abs

Preparation of H type nateglinide crystal Chen, Songnian; Feng, Qianjian; Yu, Yingmin Hangshow Pollen Co., Ltd., Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, CONEN: CNEES ANSWER 1 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 2007:14393 HCAPLUS 146:163387 ACCESSION NUMBER: DOCUMENT NUMBER:

DOCUMENT TYPE:

PATENT ASSIGNEE (S):

INVENTOR(S):

5pp.

Patent Chinese

LANGUAGE: FAMILY ACC. NUM. COUNT:

searched 5/2/07 Page 73

10/507255 SALTS OF NATEGLINIDE - STR salt Search

PATENT INFORMATION:

|                 | ıaa   | atio of<br>H type  |
|-----------------|---|--|
| DATE            | 20060721                                      | anine to e crude volume r oring trating, type obtain l al has g  |
| APPLICATION NO. | CN 2006-10052617<br>CN 2006-10052617<br>387   | The title method comprises the steps of: (1) condensing trans-4-sopropyloylohoxanecarbonyl chloride with D-phnylalanine to obtain crude crystal of B type nategilnide, (2) dissolving the crude crystal in the solution of methanol, aminomethane and water (volume ratio of 60:20:20), heating to 40-60°C, adding 2½ active carbon, decoloring for 7-15 min, filtrating, cooling to 10°C to precipitate, filtrating, and animal with 40% ethanol till neutral, and drying to obtain H type nategilnide crystal, and (3) recrystg, the mother solution to obtain H type nategilnide crystal. The product of H type nategilnide crystal has good physiol. activity. |
| DATE            | 20070103<br>A 20070103<br>CASREACT 146:163387 | the steps<br>necarbonyl<br>type nateg<br>type nateg<br>(°C, addin<br>cooling to<br>ill neutra<br>3) recryst<br>product of  |
| KIND            | A<br>CASREP                                   | omprises<br>/clohexa<br>al of B<br>ltion of<br>to 40-6<br>rating,<br>thanol t<br>thanol t<br>the (' and ('   |
| PATENT NO.      | CN 1887858 PRIORITY APPLN. INFO.:             | AB The title method comprises the steps of: (1) condensing trans-4-isopropylcyplokaancearbonyl chloride with D-ph obtain crude crystal of B type nateglinide, (2) dissolver crystal in the solution of methanol, aminomethane and we 60:20:20), heating to 40-60'C, adding 2% active carbon, for 7-15 min, filtrating, cooling to 10'C to precipitate washing with 40% ethanol till neutral, and drying to oblinateglinide crystal, and (3) recrystg, the mother solution nateglinide crystal. The product of H type nateglinide physiol.  |

146:82189
Preparation of L-threonine derivatives with high therapeutic index chandran, V. Ravi U.S. Pat. Appl. Publ., 60pp., Cont.-in-part of U.S. Ser. No. 343,557.
CODEN: USXXCO
Patent
English HCAPLUS COPYRIGHT 2007 ACS on STN 2006:1339720 HCAPLUS LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L4 ANSWER 2 OF 46 H ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(S): PATENT ASSIGNEE(S): DOCUMENT TYPE:

| PATENT NO.            |     | KIND | н   | DATE     |     | ~   | THAT  | APPLICATION     | NO   | NO.    |     | ă    | ATE      |     |
|-----------------------|-----|------|-----|----------|-----|-----|-------|-----------------|------|--------|-----|------|----------|-----|
| TIC 2006287244        |     | [4   |     | 10011221 | 221 |     | 12 2  | 2006-442027     | 1420 |        |     | ič   | 20060526 | 200 |
| WO 200505515          |     | 1 Z  |     | 0050     | 526 |     | 200   | 40 2004-US24901 | 1524 | 901    |     | , č  | 20040729 | 23  |
| W: AE, AG,            | ĄŢ, |      |     | AU, AZ,  | AZ, | BA, | BB,   | BG,             | BR,  | BW,    | BY, | BZ,  | ð        | CH, |
|                       | g,  |      |     | 표,       | Ğ,  | ¥.  | DZ,   | ъ,              | EE,  | EG.    | ES, | FI,  | 8        | gD, |
|                       | ĕ   |      |     | ID,      | IL, | IN, | IS,   | JP,             | Α̈́  | KG,    | KP, | Ř,   | KZ,      | i,  |
|                       | rs, |      |     | Ľ        | Æ   | Ð   | WG,   | Ř               | ₹    | X.     | X   | , 2M | Ř        | NI, |
|                       | ĕ.  |      |     | PL,      | E,  | 80, | RO,   | SC,             | SD,  | SE,    | SG, | SK,  | SI,      | SY, |
|                       | IN. |      |     | TZ.      | UA, | ng. | us,   | UZ,             | ν,   | Z.     | XO, | 2A,  | ZW,      | ΜZ  |
|                       | Æ   |      |     | ¥        | ΜΖ, | NA, | SD,   | SI,             | , ZS | TZ,    | ď,  | 2M,  | , MZ     | AM, |
|                       | KG, |      |     | RU,      | 13, | Ξ   | AT,   | BE,             | BG,  | CH,    | ť   | ÇZ   | 띮        | DK, |
|                       | FI, |      |     | g,       | HO, | E,  | IT,   | E               | Ä,   | NT,    | PL, | PT,  | RO,      | SE, |
| SI, SK,               | TR, | BF,  | BJ, | G.       | ე   | r,  | ક     | ð               | ß    | g<br>G | .8  | Σ    | Ř,       | NE, |
|                       | TG  |      |     |          |     |     |       |                 |      |        |     |      |          |     |
| ~                     |     | Al   | .,  | 20061026 | 026 | ٦   | US 2  | 2006-343557     | 3435 |        |     | Ñ    | 0000130  | 130 |
| PRICRITY APPLN. INFO. |     |      |     |          |     |     | 35 20 | 2003-491331P    | 1913 | 31P    |     | 5    | 20030729 | 129 |
|                       |     |      |     |          |     |     |       |                 |      |        |     |      |          |     |

US 2003-49131P P 20030729
WO 2004-1925491 AZ 20040729
WO 2004-1925491 AZ 20040729
US 2006-343557 AZ 20040729
US 2006-343557 AZ 20040729
The invention is directed to novel therapeutic compds. comprised of an L-threonine bonded to a medicament or drug having a hydroxy, amino, carboxy or acylating function. These high-therapeutic index derivs. have the same utility as the drug from which they are made and they have enhanced pharmacol. and pharmaceutical properties, with the addnl. advantage of separating various enantiomeric and diastereomeric drugs into their individual isomers. The examples describe the synthesis and AB

activities of L-threonine derivs. of (1)- and (+)-(S)-ibuprofen, (i)- and (+)-(S)-ketoprofen, (-)-(S)-ketorolac, aspirin, and fenofibric acid. The synthesis and activity of several L-serine and L-hydroxyproline analogs were also described. Thus, thy hydrochloride of (+)-(S)-ibuprofen ester of L-threonine was prepared, and its free base examined for analgesic, gastric mucosal irritation, toxicity, and pharmacokinetic properties.

Process for the preparation of nateglinide, preferably in B-form  $% \left\{ 1,2,\ldots \right\}$ Vigano, Enrico; Pizzatti, Enrica; Lanfranconi, Simona; Molteni, Renato; Landonio, Ernesto L4 ANSWER 3 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACESSION NUMBER: 2006:657506 HCAPLUS DOCUMENT NUMBER: 145:103952 U.S. Pat. Appl. Publ., 22 pp. CODEN: USXXCO Italy PATENT ASSIGNEE (S) : DOCUMENT NUMBER: TITLE: INVENTOR(S):

English Patent DOCUMENT TYPE:

20050103 20050103 APPLICATION NO. US 2005-28283 US 2005-28283 CASREACT 145:103952 20060706 DATE KIND A1 FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PRIORITY APPLN. INFO.: OTHER SOURCE(S): US 2006148902 PATENT NO.

The invention relates to a process for the preparation of nateglinide, preferably in B-form, substantially free from the H-form, comprising three steps starting from (i) reaction in an organic solvent between b-phenylalanine Me ester or a salt and trans-4-isopropylcyclohexancarboxylic acid in the presence of an acyl chloride or achonyldininadazole, optionally isolating the nateglinide Me ester or betained and re-dissolving it in a second organic solvent, (ii) addition of water and alkali hydroxide to the reaction mixture and separation of the

phase containing the alkali salt of nateglinide, and (iii) addition of hydrochloric acid to the aqueous phase from step (ii) to obtain nateglinide. In an example, the reaction was carried out in acetone in the presence of triethylamine and Et chloroformate and hydrolysis of nateglinide Me ester was carried out using toluene, tricaprylmethylammonium chloride, and aqueous potassium hydroxide to afford nateglinide in B-form (130.44°C). adneons

L4 ANSWER 4 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2006:328161 HCAPLUS DOCUMENT NUMBER: 145:173833

TITLE: Direct separation and enablication.

Direct separation and enantioseparation of nateglinide stereoisomers by HPLC Yin, Yanjie; Zhang, Qlming; Li, Huiyi; Ning, Baoming; Liu, Menying; Tian, Songjiu China Pharmaceutical University, Nanjing, 210009, CORPORATE SOURCE: AUTHOR (S):

Peop. Rep. China Yaowu Fenxi Zazhi (2005), 25(6), 657-659 CODEN: YFZADL; ISSN: 0254-1793 Yaowu Fenxi Zazhi Bianji Weiyuanhui PUBLISHER:

Chinese
AB An HPLC method was developed to sep. the enantiomers of nateglinide as well as trans-nateglinide and cis-nateglinide. The nateglinide

Journal

DOCUMENT TYPE:

SOURCE:

searched 5/2/07 Page 75

# 10/507255 SALTS OF NATEGLINIDE - STR salt Search

The enantiomers, trans-nateglinide and cis-nateglinide were directly separated on a HPLC chiral stationary phase consisting of the Kromasil TBB with hexane-2-propanol-acetic acid (95.5:0.2) as eluent and a flow rate of 0.6 mL.min-1 at 250 mm and 20°C. Three kinds of Nateglinide could be completely separated, and the resolns. were 2.38 and 1.85, resp. The method can be used for separating the nateglinide enantiomers, trans-nateglinide and cis-nateglinide and determining content of nateglinide.

One-pot process for the preparation of nateglinide Kankan, Rajendra Narayanao, Roo, Dharmaraj Ramchandra: Singh, Manjinder; Birari, Dilip Ramdas Cipla Limited, India: Wain, Christopher Paul POTI Int. Appl., 32 pp. HCAPLUS COPYRIGHT 2007 ACS on STN 2005:1328488 HCAPLUS 144:51894 English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: ANSWER 5 OF 46 PATENT ASSIGNEE (S): L4 ANSWER 5 OF 4 ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR (S): SOURCE:

APPLICATION NO. PATENT NO.

CA, CH, GB, GD, KR, KZ, MZ, NA, SG, SK, VN, YU, 20050608 SD, SC, WO 2005-GB2267 ₹8,8,8, Ϋ́Θ, YΘ, IS, MD, PT, TZ, 20051222 TR, TR, i i i i i i CZ, AM, CCU, HR, LLS, NZ, TJ, , BE, BG, , IT, LI, IS, IT, L)
PRIORITY APPLN. INFO.: AU 2005252002 CA 2570041 EP 1765769 WO 2005121071 RW:

A one-pot process for the preparation of nateglinide is presented which comprises amidation of a Cl-4 alkyl ester of D-phenylalanine, either as the free base or in salt form (typically the hydrochloride), with trans-4-isopropylcyclohexanecarboxylic acid or its acid halides to obtain a Cl-4 alkyl ester of nateglinide, preferably the Me ester of nateglinide, preferably the yield nateglinide (m.p. 128-131°). THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT OTHER SOURCE(S): REFERENCE COUNT:

2005:1261034 HCAPLUS 144:23128 Stable nateglinide form b compositions via ANSWER 6 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN L4 ANSWER 6 OF A DOCUMENT NUMBER

| crystallization<br>Venkataraman, Sundaram; Narsapur, Sharat Pandurang;<br>Kharkar, Manoj Ramesh; Bangarubabu, Rongali; Sandeep,<br>Mchantv: Savantani. Pyne: Raiu. Kakarlanudi Ranna | Dr. Reddy's Laboratories Ltd., India; Dr. Reddy's Laboratories, Inc. | PCT Int. Appl., 14 pp. | Patent<br>English           |  |
|--|--|------------------------|-----------------------------|--|
| A K  | Dr   | 2 8                    | Pat                         | <b>→</b>                                       |
| INVENTOR(S):   | PATENT ASSIGNEE(S):  | SOURCE:                | DOCUMENT TYPE:<br>LANGUAGE: | FAMILY ACC. NUM. COUNT:<br>PATENT INFORMATION: |

| PAT      | PATENT 1 | NO.        |       |     | KIND     | _   | DATE    |        | г., | APPLICATION NO. | CATI         | No    | 0    |              | ä   | DATE     |             |  |
|----------|----------|------------|-------|-----|----------|-----|---------|--------|-----|-----------------|--------------|-------|------|--------------|-----|----------|-------------|--|
| 9        | 2005     | 2005113485 | 35    |     | F Z      |     | 2005120 | 201    |     | 20 20           | 0 2005-US17  | 13176 | 64   | )<br> <br> - | %   | 20050520 | 20          |  |
|          | 3        | AE,        | AG,   | AL, | AM,      | AT, | AU,     | AZ,    | BA, | BB, BG, BR,     | BG,          | BR,   | BW,  |              | ВZ, | ð        | CH,         |  |
|          |          | Š          | 8     | CR, | GG<br>CG | CZ, | DE,     | Ķ,     | ¥,  | DZ,             | EC,          | E,    | EG,  |              | FI, | В,       | g,          |  |
|          |          | Œ,         | GH,   | ₽,  | HR,      | HO, | ID,     | II,    | ï,  | IS,             | JP,          | 떬     | ĸĠ,  | ₹            | KP, | 8        | ΚΖ,         |  |
|          |          | rc,        | ĽĶ,   | LR, | rs,      | Ξ,  | ro,     | ,<br>, | Ä,  | ð               | MG,          | Ř,    | ĕ    |              | Ř   | M2,      | NA,         |  |
|          |          | NG,        | NI,   | Š,  | NZ,      | ₹,  | PG,     | PH,    | PL, | PT,             | RO,          | Ж,    | sc,  |              | SE, | SG,      | SK,         |  |
|          |          | SI,        | SM,   | SX, | TJ,      | Ę   | ŢN,     | TR,    | Ŧ,  | TZ,             | ďĄ,          | ug,   | ns,  |              | ď,  | Š        | χΩ <b>,</b> |  |
|          |          | ZA,        | ZM,   | ZW  |          |     |         |        |     |                 |              |       |      |              |     |          |             |  |
|          | R.       | BW,        | GH,   | ğ   | Α,<br>Έ  | ĽS, | ΜW,     | М2,    | NA, | SD,             | SI,          | , 2S  | , ZT | ug,          | ζΜ, | ZW,      | AM,         |  |
|          |          | A2,        | BY,   | KG, | K2,      | ð   | RU,     | TJ,    | Ĭ,  | AT,             | BE,          | BG,   | CH,  | CY,          | CZ, | DE,      | Ď,          |  |
|          |          | EE,        | ES,   | FI, | FR,      | B   | GR,     | HO,    | IE, | is,             | II,          | ij,   | ĽŪ,  | ÄĊ,          | Ŋ,  | PI,      | PT,         |  |
|          |          | R0,        | SE,   | SI, | SK,      | Ŧ,  | BF,     | BJ,    | GF, | G               | CI,          | ₹     | g,   | ₽,           | ĝ   | ₹        | М,          |  |
|          |          | ¥,         | NE,   | SN, | TD,      | 13  |         |        |     |                 |              |       |      |              |     |          |             |  |
| PRIORITY | APPLN.   | EN.        | INFO. |     |          |     |         |        | Þ   | IS 20           | 04-5         | 7268  | 9P   | -            | 2   | 0405     | 20          |  |
|          |          |            |       |     |          |     |         |        | Þ   | <b>US</b> 20    | 2004-586431P | 8643  | 1.   | ш,           | 2   | 20040708 | 80          |  |
|          |          |            |       |     |          |     |         |        | ₽   | IS 20           | 05-6         | 4461  | 4P   |              | ~   | 0501     | 18          |  |
|          |          |            |       |     |          |     |         |        |     |                 |              |       |      |              |     |          |             |  |

AB A process for preparing nateglinide Form B comprises dissolving nateglinide (I) in a solvent and adding the solution, at temps. of  $40-45^\circ \text{C}$ , to a hydrocarbon liquid that is at temps. of  $40-45^\circ \text{C}$ . Then, water is added and the mixture is allowed to cool, producing crystals of nateglinide Form B.

L4 ANSWER 7 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:
144:11582
DOCUMENT NUMBER:
17ILE:
Frocess for the preparation of polymorphic crystalline
forms of nateglinide ammonium salt
NUENTOR(S):
PATENT ASSIGNEE(S):
PATENT ASSIGNEE(S):
Pharmaccuticals Usa, Inc.
SOURCE:
PCT Int. Appl., 25 pp.

Page 77 searched 5/2/07

## 10/507255 SALTS OF NATEGLINIDE - STR salt Search

CODEN: PIXXD2 Patent English

DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

| APPLICATION NO. DATE | 005-US16343 BG, BR, BW, BY EC, EE, EG, ES JP, KE, KG, KM MG, MK, MM, MW RO, RU, SC, SD UA, UG, US, UZ | SL, SZ, TZ, UG, ZM, ZM, AM, BE, BG, CH, CY, CZ, DE, DK, TT, LT, LU, MC, NL, PL, PT, COS-2065-2863793 20050509 2005-286370 20050509 2005-186381 20050509 7, IT, LI, LI, LI, LS, MC, PT, TR, BG, CZ, EE, HU, PL, SK, | 20070418 CN 2005-80014509 20050509 US 2004-569047P P 20040507  MO 2005-US16343 W 20050509  phic crystalline forms of nateglinide ammonium salt THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT | nalogs and their<br>un; Han, Han; Gon<br>ig<br>and Toxicology, A<br>Beijing, 100850,  | E: Shongguo Yaowu Huaxue Zazhi (2004), 14(6), 335-339, 362<br>COEDE: ZYHZEF, ISSN: 1005-0108  SHER: Chongguo Yaowu Huaxue Zazhi Bianjibu Journal Chinese SOURCE(S): CASREACT 145:315230 Ahaloga of nateglinide [l.e., N-[[trans-4-(1-methylethyl) cyclohexyl]carbon y]]-phenylalanine] were synthesized, and their biol. activities were tested by glycemia levels in mice. The new compds. were synthesized using N-[isopropyl]piperazine, N-isopropyl-4-piperazine, N-stopropyl-4-piperidincarboxylic acid, Irans-4-dimethylamino-1-cyclohexanecarboxylic acid and substituted phenylalanine as the starting materials. The biol. activities of the new compds. were tested by the glycemia levels in mice via drug administration |
|----------------------|---|--|--|---|--|
| APP                  | MO 2<br>BA, BB,<br>DM, DZ,<br>IN, IS,<br>MA, MD,<br>PL, PT,   | NA, SI<br>TM, AI<br>IE, IS<br>CF, CG<br>CA<br>US<br>EP<br>GB, GR   | CN US WO :alline   | iGHT 2007 ACS on 5 HCAPLUS of nateglinide an ion nxin. Dong, Junju jie; Liu, Keliang of Pharmacology a edical Sciences,   | Huaxue (185N: 1) Huaxue (1852) Fans-4- ed, and (1860) The nel (1860) The nel (1860) The nel (1860)   |
| DATE                 | 20051124<br>AU, AZ,<br>DE, DK,<br>ID, IL,<br>LU, LV,<br>PG, PH,                                       | MW, MZ,<br>RU, TJ,<br>GR, HU,<br>BF, BJ,<br>20051124<br>20060105<br>20060517<br>ES, FR,<br>RO, MK,   | YU A 20070418 CN 2 NO 2 POO 1 MO 2 polymorphic crystalline 12 THERE ARE 12 CITE RECORD. ALL CITAT  | ULS COPYRIGHT 2007 ACS or 2005:841495 HCAPLUS 146:313230 Synthesis of nateglinide edetermination Janxin; Dong, Junjang, Shijie; Liu, Kelian Huang, Shijie; Liu, Kelian Institute of Pharmacology Military Medical Sciences, China | JEONGGUO Yaowu Huaxue Zazhi 362<br>CODEN: ZYHZEF; ISSN: 1005-01<br>Zhongguo Yaowu Huaxue Zazhi<br>Journal<br>Chinese<br>CASREACT 145:315230<br>Ge lie., N'I(trans-4-(1-met)<br>were synthesized, and their<br>evels in mice. The new comp<br>in. N'isopropyl-4-piperidin.<br>o-1-cyclohexanecarboxylic ac<br>starting materials. The bi<br>by the glycemia levels in mi  |
| KIND                 | A1<br>CU, CZ,<br>HR, HU,<br>LS, LT,<br>NZ, OM,  | LS, TR, TR, TR, TR, TR, TR, TR, TR, TR, TR   | YU<br>A<br>Olymorp<br>12 T   | CC<br>5:84<br>:31:<br>:31:<br>ng,<br>ng,<br>titu  | Zhongguo 362 362 ZCODEN: ZY Zhonguo Journal CASREAT GASREAT Were syr were syr evels in evels in evels in evels of zhonguo starting   |
| ×                    |   | XXFOH DH   |  | HCAPLUS<br>200<br>200<br>145<br>Syn<br>det<br>2ha<br>2ha<br>Hua<br>Hua<br>Hua<br>(hai   | 2<br>3<br>3<br>2<br>2<br>4<br>5<br>6<br>6<br>6<br>7<br>6<br>7<br>7<br>8<br>8<br>8<br>9<br>9<br>1<br>9<br>1<br>9<br>1<br>9<br>1<br>9<br>1<br>9<br>1<br>9<br>1<br>9<br>1   |
|                      | SK, CH, CH, CH, CH, CH, CH, CH, CH, CH, CH  | ZM,<br>GH,<br>BY,<br>ES,<br>SE,<br>NE,<br>NE,<br>NE,   | , HR, I<br>INFO.:<br>glycemi<br>ed   | # K. " E.   | na<br>11y<br>e e e t   |
| PATENT NO.           | WO 2005110972<br>W. AE, PA<br>CN, C<br>GE, G<br>IC, LI<br>IC, LI<br>NG, N                             | RW: BW, CA, CZ, CZ, CZ, CZ, CZ, CZ, CZ, CZ, CZ, CZ   | BA, HR, IS, CN 1950331 PRIORITY APPLN. INFO.: AB Anti-hyperglycemic are prepared REFERENCE COUNT:  | 14 ANSWER 8 OF ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: AUTHOR(S): CORPORATE SOURCE:   | SOURCE: Shongguo Yaowu Huaxue Zazh SOURCE: 362 CODEN: ZYHZEF; ISSN: 1005-CODEN: ZYHZEF; ISSN: 1005-CODEN: ZYHZEF; ISSN: 1005-CODEN: ZYHZEF; ISSN: 1005-CODEN: ZYHZEF; ISSN: 1005-COTHER SOURCE(S): CASREACT 145:315230 AB Analogo of nateglinide [i.e., N-[[trans-4-(1-man-4-chenylalanine] were synthesized, and the tested by glycemia levels in mice. The new co N-[isopropyl]piperazine, N-isopropyl-4-piperid trans-4-dimethylamino-1-cyclohexanecarboxylic phenylalanine as the starting materials. The compds: were tested by the glycemia levels in  |

Page 78 searched 5/2/07

after forbiddance of food-intake and oral delivery of glucose. Forty-three new compages, were synthesized, and their structures were confirmed by elementary anal., IR, polarimetric anal., IH-NNR and MS. compound, 4-fluoro-N-[[4-(1-methylethyl)-1-piperazinyl]carbonyl]-L-phenylalanine monohydrochloride, showed significant hypoglycemic effect on glycemia of mice, and had an (\$)-configuration at the chiral center, which was opposite to the control.

L4 ANSWER 9 OF 46 HCAPLUS COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:476519 HCAPLUS
DOCUMENT NUMBER: 143:97635
TITLE: agent nategilinde
INVENTOR(S): 2hong, Bohus; Mu, Bo; Yan, Yuan
PATENT ASSIGNEE(S): 7oxic Drug Inst., Academy of Military Medical Science, PLA, Peop. Rep. China Fantus Zhung, Zhung, Zhunii Shenqing Gongkai Shuomingshu, No pp. GODEN: CNXEV DOCUMENT TYPE: CODEN: CNXEV PATENT TAPE: CHINES CHINE

PATENT NO. KIND DATE APPLICATION NO. DATE

CN 151735

PRIORITY APPLN. INFO.:

CASREACT 143:97635

AB A scalable process for the preparation of nateglinide, a hypoglycemic agent, was reported. The key improvement is that the acylation of D-phenylalanine with 4-isopropylcyclohexanecarbonyl chloride was performed under a homogeneous condition using a mixture of dioxane or THF and H2O as solvent, largely increasing the yield. Other features include the use of cheap Pd/C instead of previously expensive PtO2 as hydrogenation catalyst in the reduction of 4-isopropylbenzoic acid into 4-isopropylcyclohexanecarboxylic acid. Purification of nateglinide by recrystn. in petroleum ether, hexane and cyclohexane or their mixts. is claimed.

Improved process for the preparation of hypoglycemic agent nateglinide
Zhu, Qin: Pan, Junfang: Shi, Mingfeng
Shanghai Huashuo Medicine Science & Technology
Devalopment Co., Ltd., Peop. Rep. China
Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. 20030117 DATE APPLICATION NO. CN 2003-114970 CN 2003-114970 HCAPLUS COPYRIGHT 2007 ACS on STN 2005:476518 HCAPLUS 143:26875 20040804 CODEN: CNXXEV DATE Chinese Patent KIND Ø FAMILY ACC. NUM. COUNT: PATENT INFORMATION: ANSWER 10 OF 46 CN 1517334 PRIORITY APPLN. INFO. PATENT ASSIGNEE (S): L4 ANSWER 10 OF ACCESSION NUMBER: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR (S): SOURCE:

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# 10/507255 SALTS OF NATEGLINIDE - STR salt Search

A process for the preparation of nateglinide comprises: (I) the amidation reaction in a first organic solvent between D-phenylalanine Me ester, or a salt, and trans-4-isopropylcyclohexanecaboxylic acid and an acyl chloride, or carbonyldimidazole, to obtain the nateglinide Me ester; (Ia) optionally isolating the nateglinide Me ester and redissolving it in a second organic solvent to give a solution; (II) addition of water and alkali hydroxide to the reaction mixture coming from step (I) without isolating the nateglinide Me ester, or, if applicable, to the solution of step (Ia), and separation of the aqueous phase containing the alkali salt of nateglinide; AB A scalable process for the preparation of nateglinide, a hypoglycemic agent, was reported. The key improvement is that the acylation of D-phenylalanine with 4-isopropylcyclohexanecarbonyl chloride was performed under a homogeneous condition using a marture of DWF and RZO as solvent, largely increasing the yield. Other features include the use of cheap Pd/C instead of previously expensive PtO2 as hydrogenation catalyst in the reduction of 4-isopropylbenzoic acid into 4-isopropylcyclohexanecarboxylic of hydrochloric acid to the aqueous phase coming from step (II) to obtain nateglinide , wherein the organic solvent employed in step (II) is a water non-miscible solvent.

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS Process for the preparation of the crystalline B-form nateglinide from D-phenylalanine methyl ester and trans-4-isopropylcyclohexanecarboxylic acid Vigano', Enrico: Pizzati, Enrica: Lanfranconi, Simona; Molteni, Renato; Landonio, Ernesto A.M.S.A. Anonima Materie Sintetiche e Affini S.p.A., THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT A1 2005061 EP 2003-2....
B1 20061227
B2, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
LV, FI, RO, MK, CY, AL, TR, BG, C2, EE, HU, SK
T 20070115 EP 2003-27114 A 20031126 Preparation of alanine derivative as antidiabetics Yang, Yushe; Tang, Lei; Ji, Ruyun; Chen, Kaixian Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China APPLICATION NO. ANSWER 11 OF 46 HCAPIUS COPYRIGHT 2007 ACS on STN SION NUMBER: 2005:467801 HCAPIUS 143:7982 HCAPLUS COPYRIGHT 2007 ACS on STN Eur. Pat. Appl., 32 pp. CODEN: EPXXDW 2005:414565 HCAPLUS 142:482315 English Patent Italy KIND FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PRIORITY APPLN. INFO.: OTHER SOURCE(S): L4 ANSWER 12 OF 46 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE(S): INVENTOR(S): PATENT ASSIGNEE(S): L4 ANSWER 11 OF ACCESSION NUMBER: DOCUMENT NUMBER: EP 1535900 EP 1535900 REFERENCE COUNT: PATENT NO. AT 349418 (III) addition DOCUMENT TYPE: INVENTOR (S): SOURCE: AB

Page 80 searched 5/2/07

Faming Zhuanli Shenqing Gongkai Shuomingshu, 26 pp. CODEN: CNXXEV Patent Chinese 20030124 A 20030723 CN 2003-115160 CN 2003-115160 CASREACT 142:482315; MARPAT 142:482315 APPLICATION NO. 20030723 DATE KIND DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PRIORITY APPLN. INFO.: OTHER SOURCE(S): GI CN 1431197 PATENT NO.

Alanine derivs. I (RI = 2-(1-indoly1)ethy1, 2-[N-(2-benzoxazoly1)-N-methy1)aminoethy1, 2-(N-methy1-N-methy1)aminoethy1, 2-(N-methy1-N-methy1)aminoethy1, 2-(N-methy1-2-pheny1-4-oxazoly1)ethy1, 4-trifluoromethy1benzy1, benzy1; R2 = H, alky1) is prepared by condensation reaction of trans-4-isopropy1cyclohexanecarboxy1ic acid N-succinimidy1 ester with Loor b-tyrosine Me ester in inert solvent to obtain 3-(4-bydroxybeny1)-2-(trans-isopropy1cyclohexylcarboxamido)propanoic acid Me ester (II), Mitsunobu reaction with aromatic alc., and then hydrolysis with inorg. base solution The method may be prepared by (1) etherification of II with allide in alkaline medium; (2) hydrolysis of II; or (3) condensation reaction of II with amino-protected 2-methylaminoethanol, condensation reaction with 2-fluoropyridine, and hydrolysis with base. The alanine derivative and diabetes mellitus. ΑB

and therapy Yang, David J.; Oh, Chang-sok; Kohanim, Saady; Yu, Dong-Fang; Azhdarinia, Ali; Bryant, Jerry Board of Regents, the University of Texas System, USA PCT Int. Appl., 67 pp. Mechanism-based targeted pancreatic beta cell imaging ANSWER 13 OF 46 HCAPIUS COPYRIGHT 2007 ACS on STN SION NUMBER: 2005;283370 HCAPIUS ENT NUMBER: 142:331961 PATENT ASSIGNEE(S): L4 ANSWER 13 OF ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(S):

DOCUMENT TYPE: LANGUAGE:

SOURCE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

searched 5/2/07 Page 81

## 10/507255 SALTS OF NATEGLINIDE - STR salt Search

searched 5/2/07

Page 82

ANSWER 15 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN

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2005:204069 HCAPLUS
142:482313
Preparation of aromatic amino acid derivatives for treatment of blood sugar disorders
Liu, Keliang; Pan, Mangen; Liang, Yuanjun; Zhong, Bohua; Li, Bihai; Huang, Shijie; Li, Xin; Dong, Huajin; Chi, Mugen
Institute of Toxicant and Pharmaceuticals, Academy of Military Medical Science of PLA, Peop. Rep. China Faming Zhuani Shenqing Gongkai Shuomingshu, 41 pp. PATENT ASSIGNEE(S): ACCESSION NUMBER: DOCUMENT NUMBER: INVENTOR (S): SOURCE: TITE:

Chinese Patent

DOCUMENT TYPE:

DATE KIND æ CN 1453265
PRIORITY APPLN. INFO.:
OTHER SOURCE(S): LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT NO.

20030425 DATE 4 CASREACT 142:482313, MARPAT 142:482313 APPLICATION NO. CN 2003-123272 CN 2002-116715 20031105

Y-CO-NH-CH-(CH2)n-Ar

The aromatic amino acid derivs. I [n = 0, 1; X, Y = C, N; Ar = benzene ring substituted by one or more substituents (such as halo, NO2, OH, COZH, CF3, trifluoromethoxy, methylenedithio, alkyl, alkenyl, ester group, methylenedithio, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkenyl, alkenoxy, alkenoxy, phenoxy, benzyloxy, ester group, amino, amido), other aromatic ring, heterocyclic ring or its substituted derivative), useful for the treatment of blood sugar disorders, were prepared by acylation of 3-arylalanine RCl with 4- isopropylcyclohexylcarbonyl chloride or 1-isopropyl-4-piperidinylcarbonyl chloride. Thus, reaction of 2-3-ditrophenylalanine hydrochloride with aqueous NaOH at room temperature for 5 h gave, after acidification with aqueous HCl æ

71.1% N-(trans-4-isopropylcyclohexanecarbonyl)-D-3-nitrophenylalanine (II). II showed endothelin receptor antagonist activity at 10-9mol/L

HCAPLUS COPYRIGHT 2007 ACS on STN 2005:59980 HCAPLUS 142:141296 Crystalline form of nateglinide Frenkel, Gustavo; Gome, Boaz; Wizel, Shlomit L4 ANSWER 16 OF 46 ACCESSION NUMBER: DOCUMENT NUMBER:

Israel
U.S. Pat. Appl. Publ., 91 pp., Cont.-in-part of U.S.
C.E. No. 622,905.
CODEN: USXXCO INVENTOR(S):
PATENT ASSIGNEE(S):
SOURCE:

English DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

searched 5/2/07 Page 83

# 10/507255 SALTS OF NATEGLINIDE - STR salt Search

| DATE            | 20031224<br>2003113<br>20040113<br>20040113<br>20040113<br>20040113<br>20040113<br>20040113<br>20040113<br>20040113<br>20040113<br>20040113<br>20060105<br>P 20030224<br>P 20030224<br>P 20030224<br>P 20030224<br>P 200201105<br>P 20030118         | r preparation, as well rof administration are nateglinide comprises (cetate, (b) seeding the the crystalline form as it 99% pure. For les, or Et acetate at as obtained. Form Z was with 185 m (3.5 was with 180 m), while stirring at was washed with toluene was washed with water product, which lost it y >99%, yield   |
|-----------------|---|---|
| APPLICATION NO. | US 2003-746697 US 2003-746697 US 2003-746697 US 2003-746697 US 2004-USSB39 WO 2004-USSB39 WO 2004-USSB39 WO 2004-USSB39 WO 2003-74909 US 2003-449791P US 2003-442950P US 2003-442950P US 2002-414199P US 2002-412950P US 2002-412950P US 2002-412950P US 2003-412950P US 2003-4146699 | tenses for thei<br>liline form of<br>liline form of<br>liline form of<br>plinide in Et a<br>(c) recovering<br>more than abou<br>litrile, aceton<br>lear solution w<br>poration at ab<br>Form B. Also,<br>anine (PheOH)<br>ca afford a cla<br>trans-4.<br>CHAC, 9.02 g,<br>above, over in<br>the funnel<br>was stirred for<br>me pH to 3, whill<br>in the solid was<br>3 of the moist  |
| KIND DATE       | All 20040916 All 20040916 All 20040916 All 20040912 All 20040912 All 20040912 AL AM, AT, AU, AZ, CR, CU, CZ, DE, DE, DE, DE, DE, DE, DE, DE, DE, DE   | crystalline forms of nateglinide and processe pharmaceutical formulations containing them a provided. A process for preparing crystallin steps of (a) preparing a solution of nateglinic solution with nateglinide crystals, and (c) precipitate The nateglinide crystals, and (c) and action of a solution of nateglinide of a solution of law north about 55° in over about 15° min until a clear about 55° in over about 15° min until a clear aming to give dry nateglinide crystalline Form prepared by treating 7.73 g of D-phenylalanin corresponding Na-salt. A solution of neat to added to the solution of Phe-HH obtained about temperature The resulting mixture was treated with 10% HCl (12 mL) to adjust the pinkture was stirred for 1 h, and filtered. 16700 mL) and sucked well to afford 33.3 g of 668). |
| PATENT NO.      | NFO.  | as pharmaceutical formulate provided. A process for the steps of (a) preparing a solution with nateglinia example.  example precipitate The nategliniate (5 g) was cabout 55° in over about The solvent was removed manify to give dry nategly prepared by treating 7 equiv) of 3.5% NaOH at corresponding Na-salt. isopropylcyclohexanecat added to the solution crom temperature The 1 isopropylcyclohexanecat added to the solution crom temperature The 1 in 3) and added. The treated with 10% HCl (7 mixture was stirred foo (200 mL) and sucked well weight after drying at 86%).  |
|                 | PRIO  | AB as as exam   |

Page 85 searched 5/2/07

142:317044
An efficient large scale synthesis of nateglinide
Chandraeekhar, Batchu; Sawanth, Mangesh S.; Naik,
Sameer J.; Galkwad, Nandakumar B.; Kulkarni, Pramila
V.; Bhirud, Shekar B.
Process Research and Development, Glenmark Research
Centre, MIDC Mahape, Navi Mumbai, 400709, India
Organic Preparations and Procedures International
(2004), 36(5), 459-467

CORPORATE SOURCE:

TITLE: AUTHOR(S):

14 ANSWER 18 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:937572 HCAPLUS DOCUMENT NUMBER: 142:317044

10/507255 SALTS OF NATEGLINIDE - STR salt Search

46 HCAPLUS COPYRIGHT 2007 ACS on STN
2004:648495 HCAPLUS
111:17476
Preparation of alamine compounds as antidiabetics
Yang, Yushe; Tang, Lei; Ji, Ruyun; Chen, Kaixian
Shanghai Institute of Materia Medica, Chinese Academy
of Sciences, Peop. Rep. China
PCT Int. Appl., 28 pp.
CODEN: PIXXD2
Patent
Chinese carbonate with D-phenylalanine.

ENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT Nateglinide was prepared as the desired H polymorph by reaction of trans-4-isopropylcyclohexanecarboxylic acid with ClCO2Et and treating the AM, A2, BY,
DK, EE, ES,
SK, TR, BF,
TD, TG
20030128
20030128
SE, MC, PT,
HU, SK
20030128
20030128 20030128 CH, CN, GE, GH, LK, LR, OM, PH, \$ 60,0 Kr 18,0 Kr 18,0 Kr CODEN: OPPIAK; ISSN: 0030-4948
Organic Preparations and Procedures, Inc. Journal English
CASREACT 142:317044 BZ, GB, KZ, NO, TN, Z. ES, FR, GB, GR, IT, LI, LU, NL, RO, MK, CY, AL, TR, BG, CZ, EE, 20060420 JP 2004-567216

Z. COGO713 US 2005-543091 NO 2003-CN96 ZW, DE, SI, SN, CASREACT: 141:157476; MARPAT 141:157476 BR, BY, ES, FI, KP, KR, MX, MZ, TJ, TM, UG, ZM, CY, CZ, PT, SE, MR, NE, APPLICATION NO. AU 2003-303815 EP 2003-815509 WO 2003-CN96 20040812 E, T A1 IE, SI, LT,
JP 2006513250
US 2006154970
PRIORITY APPLN. INFO.:
OTHER SOURCE(S): 49838888888 ijij, LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L4 ANSWER 19 OF 46 H ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: PATENT ASSIGNEE (S): OTHER SOURCE(S): REFERENCE COUNT: PUBLISHER: DOCUMENT TYPE: LANGUAGE: PATENT NO. DOCUMENT TYPE: INVENTOR (S): SOURCE:

Page 86 searched 5/2/07

Alanine compds. I (R1 = H, alkyl, Ph, aryl, heteroaryl, etc.; R2 = H, alkyl), uestul for treatment of type II diabetes, are prepared Thus, (28)--2-[N-(trans-4-isopropylcyclohexylcarbonyl)aminol-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionic acid was prepared and showed insulin sensitizer activity. AB

Process for the formation of a crystalline polymorphic form of nateglinide Reguri, Buchi Reddy, Kadaboina, Rajasekhar; Reddy's Laboratories Limited, India; Reddy's ANSWER 20 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN SSION NUMBER: 2004:203799 HCAPLUS 140:241062 Laboratories, Inc. PCT Int. Appl., 29 pp. CODEN: PIXXD2 Polavarapu, Srinivas PATENT ASSIGNEE(S): L4 ANSWER 20 OF ACCESSION NUMBER: DOCUMENT NUMBER: INVENTOR (S):

Patent English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

DOCUMENT TYPE:

SOURCE:

| PATENT NO.      | NO. |       |     | KIND |     | DATE    |      | 7  | APPLI  | CAT           | APPLICATION NO.   | <u>.</u> |     | ă i  | DATE     |             |
|-----------------|-----|-------|-----|------|-----|---------|------|----|--------|---------------|-------------------|----------|-----|------|----------|-------------|
|                 |     | !     |     |      |     |         | !    |    |        |               |                   |          |     |      |          | ! !         |
| 0203            |     | ڡۣ    |     | ΑI   | ••• | 20040   | 311  |    | ئ<br>2 | <b>303-</b> L | 18326             | 880      |     | ñ    | 20030827 | 127         |
| Ä,              |     | AG,   | AĽ, | Æ,   |     | AU,     | AZ,  | BA | BB,    | BG,           | BR,               | BY,      | BZ, | ð    | GH,      | 3           |
| ပ္ပ             |     | Ġ,    | 8   | ζ2,  |     | Ŗ,      | Ĕ,   | 20 | EC,    | EE,           | ES,               | EI,      | g,  | gD,  | Œ,       | GH,         |
| £               |     | HR,   | HO, | ID,  |     | IN,     | ıs,  | JΡ | Ä,     | KG,           | KP,               | 8,       | KZ, | ĽĊ,  | ĽĶ,      | LR,         |
| ĽS,             |     | ĽŢ,   | ľu, | Ľ,   | Ř   | MD, MG, | ÄĞ,  | ¥  | Ĕ      | Š             | , MN, MW, MX, MZ, | MZ,      | NI, | Š,   | NZ,      | NO, NZ, OM, |
| δ,              |     | PH,   | PL, | PT,  |     | RU,     | sc,  | SD | SE,    | sg,           | SK,               | SI,      | SΥ, | ŢĴ,  | Ξ        | ĮŅ,         |
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| FI, FR,         |     | E,    | GB, | GR,  |     | IE,     | II,  | 3  | Ř,     | Ĕ,            | PT,               | 8,       | SE, | SI,  | SK,      | TR,         |
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| 2002MA00631     |     | 31    |     | A    |     | 2005    | 304  |    | IN 20  | 302-1         | 4A631             | _        |     | 5    | 30208    | 328         |
| 2003262928      |     | 80    |     | A1   | - • | 20040   | 319  |    | AU 20  | 303-2         | 26292             | 80       |     | 5    | 3030     | 127         |
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| PRIORITY APPLN. | _   | INFO. | ••  |      |     |         |      |    | IN 20  | 302-1         | 2002-MA631        |          | 7   | A 21 | 20020828 | 328         |
|                 |     |       |     |      |     |         |      | _  | WO 20  | 003-L         | JS 268            | 88       | _   | 2    | 0030     | 327         |
|                 |     |       |     |      | •   |         | •    |    |        |               |                   |          | :   | •    |          | :           |

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT AB A crystalline polymorphic form of nateglinide are described and its X-ray diffraction pattern presented.

REFERENCE COUNT: 7 THERE ARE 7 CTUTEN DEFENDANCE.

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Page 87

## 10/507255 SALTS OF NATEGLINIDE - STR salt Search

Niu, Zhanqi; Wang, Lifang; Chen, Yujie; Shen, Dongmin Zhonqqi Pharmaceutical Technology (Shijiazhuang) Co., Litd., Peop. Rep. China PCT Int. Appl., 19 pp. CODEN: PIXXDZ Preparation of nateglinide inclusion complexes with cyclodextrins and their use in pharmaceutical DATE L4 ANSWER 21 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:203709 HCAPLUS DOCUMENT NUMBER: 140:259085 compositions DATE Chinese Patent FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE(S): DOCUMENT TYPE: INVENTOR (S): LANGUAGE: SOURCE:

20030822 A 20020827 W 20030822 CH, CO, GH, GM, LR, LS, OM, PG, TN, TR, AM, AZ, BY, DK, EE, ES, SI, SK, TR, SN, TD, TG 20020827 20030822 ZW, DE, SE, NE, 7,0°C, CN 2002-132321 AU 2003-255130 CN 2002-132321 WO 2003-CN707 APPLICATION NO. 40 2003-CN707 주, SE, SE, BB, BG, EE, ES, KG, KP, MW, MX, SG, SK, YU, ZA, SZ, TZ, BG, CH, GQ, GW, 8 E B AU, AZ, I DM, DZ, I SC, SD, UZ, VC, MZ, SD, TM, AT, TM, AT, CM, GA, 200403303 20040311 A1 2 AM, AT, DE, DK, II, IN, MA, MD, MD, WD, RU, MD, RU, RU, IS, MW, RU, TU, TU, GR, HU, GR, HU, CG, CI, A1 2 KIND REPUTATION OF THE PROPERTY OF CN 1478470 AU 2003255130 PRIORITY APPLN. INFO.: AE, AG, CR, CU, HR, HU, LT, LU, PPH, PL, TT, TZ, GH, GM, KG, KZ, KZ, KE, BJ, BF, BJ, WO 2004019989 PATENT NO. RW:

79 AB The invention relates to preparation of inclusion complexes of nategilinide, containing nategilinide and B-cyclodextrin and its derivates, particularly to nategilinide-p-cyclodextrin inclusion complexes. The preparing process comprises saturated solution method, ultrasonic method and grinding method. The inclusion complexes obtained have high stability and can be used in the manufacture of pharmaceutical formulations of nategilinide. For example, nategilinide-p-cyclodextrin (1.2) inclusion complex prepared by grinding the mixture of 10 mL nategilinide (0.0031 mol) ethanol solution and p-cyclodextrin (0.0062 mol), was incorporated into tablets together with starch, crosslinked CMC and magnesium stearate.

REFERENCE COUNT:

2 RECORD. ALL CITATIONS AVAILABLE FOR THIS REFERENCE COUNT:

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140:199745
Synthesis and purification of nateglinide
Synthesis and purification of nateglinide
Makk, Samir Jaivant, Rulkarni, Pramila Vijay; Gaikwad,
Nank, Samir Baburao; Sawant, Mangesh Shivram; Bhirud,
Shekhar; Batchu, Chandrasekhar
Glenmark Pharmaceuticals Limited, India
PCT Int. Appl., 28 pp. PLUS COPYRIGHT 2007 ACS on STN 2004:182826 HCAPLUS L4 ANSWER 22 OF 46 ACCESSION NUMBER: PATENT ASSIGNEE(S): DOCUMENT NUMBER: INVENTOR (S):

Patent English DOCUMENT TYPE: SOURCE:

FAMILY ACC. NUM. COUNT:

10/507255 SALTS OF NATEGLINIDE - STR salt Search

#### PATENT INFORMATION:

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| APPLICATION NO. | WO 2003-IB3270 |      | BG, | 핊          | KG, | ž      | SG, | χΩ  | SZ, TZ, U       | ₽,  | Z,  | ₹   | 002-      | 003-          | 2002-MU773      | 003-    |
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| NO.             | 0184           | 0184 | Ė,  | ပွဲ        | Ē   | rs,    | PG, | ŢŖ, | ĞĦ,             | ĸĠ, | FI, | BF, | 2002MU007 | 2633          | IN.             |         |
| PATENT NO.      | WO 2004018408  | 2004 | 3   |            |     |        |     |     | RW: GH, GM, KE, |     |     |     | 2002      | AU 2003263386 | PRIORITY APPLN. |         |
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OTHER SOURCE(S): CASREACT 140:199745; MARRAT 140:199745

AB N-[(trans-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine (nateglinide)
was prepared by reaction of trans-4-isopropylcyclohexylcarboxylic acid with
an alkyl chloroformate in a ketonic solvent in the presence of a base at
-20 to 30°C and reaction of the mixed anhydride product with an aqueous
alkali salt solution of D-phenylalanine. An example shows the synthesis of
nateglinide by using triethylamine and Et chloroformate in acetone (97%
pure following HPLC).

THERE ARE I CITED REFERENCES AVAILABLE FOR THIS

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

| L4 ANSWER 23 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN<br>ACCESSION NUMBER: 2004:80637 HCAPLUS<br>DOCUMENT NUMBER: 140:151932 | Preparation of polymorphic forms of nateglinide Yahalomi, Ronit; Shapior, Evgeny; Dolitzky, Ben-zion; Conian Vissal; Gram Pasz | Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceutical Usa. Inc. | PCT Int. Appl., 130 pp. CODEN: PIXXD2 |
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| L4 ANSWER 23 OF 46 ACCESSION NUMBER: DOCUMENT NUMBER:   | TITLE:<br>INVENTOR(S):   | PATENT ASSIGNEE(S):  | SOURCE:                               |

Patent English 4 DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

| PATENT N | NO.      |     |     | KIND | 0   | DATE  |      | ~    | APPLICATION | CAT | NOI | NO.             |     | ä   | ATE      |     |
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## 10/507255 SALTS OF NATEGLINIDE - STR salt Search

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| : 140:94292 Process for preparing nateglinide and its Intermediates Yahalomi, Ronit; Shapiro, Evgeny; Dolitzky, Ben-zion; Gozlan, Yigael (S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc. PCT Int. Appl., 31 pp. CODBN: PIXXD2 Patent English COUNT: 4 | KIND DATE  | CASREACT 140:94292 preparation of nateglinide involves convertively examecarboxylic acid into the acid chloride in the presence of an organic able salt of D-phenylalanine with the acid ase system or in water free of a co-solvent. THERE ARE 6 CITED REFERENCES AVAILABLE IN TRECORD, ALL CITATIONS AVAILABLE IN |
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| DOCUMENT NUMBER: TITLE: INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: FAMILY ACC. NUM. CC PATENT INFORMATION:  | MO 2004005240 MO 2004005240 MO ABC, MG MO HISTORY MO ABC, MG MO HISTORY MO ABC, MG MO HISTORY MO ABC, MG MO AB | OTHER SOURCE(S): AB A process for the trans-4-isopropylor reaction with thic acylation of a suingle or two ph REFERENCE COUNT:  |

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WO 2002-IN114

AB Novel polymorph Form C of N-(trans-4-isopropylcyclohexylcarbonyl)-D-
phenylalanine (I; i.e., nateglinide) is produced having a different IR
spectrum and X-ray diffraction patterns (presented) from previously known
forms of I.

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139:341725
Novel nateglinide crystals
Koguchi, Yoshihito; Nakao, Tomoko; Sumikawa, Michito
Ajinomoto Co., Inc., Japan
PCT Int. Appl., 17 pp.
                                       Process for the preparation of a crystal polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide) phenylalanine (nateglinide) Rajamahendra, Shanmughasamy; Aswathanarayanappa, Chandrashekar; Puthiaparampil, Tom Thomas; Sridharan, Madhavan; Ganesh, Sambasivam Biocon India Limited, India PCT Int. Appl., 19 pp.
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US 2005165108
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Page 92 searched 5/2/07

| APPLICATION NO. DATE | WO 2003087039  W. AE, AG, AL, AM, AT, BA, BB, BB, BB, BB, BB, BB, BB, BB, BB   | solution to precipitate crystals, subjecting the product to filtration, and drying at a specific temperature Nateglinide is a known antidiabetic.  In THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT |
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| DATE                 | 20031023 AT. AU, AZ, DE, DE, DE, DE, DE, DE, DE, DE, DE, IL, IN, IS, IL, IN, IS, RU, S. SD, RU, CS, SD, RU, AT, TJ, TT, AT, TJ, TT, AT, TJ, TT, AT, TJ, TT, AT, TJ, TE, IT, CI, CM, GA, 20050112 DK, ES, FR, FI, RO, MK, FI, R | rystals, su<br>erature Na<br>THERE ARE<br>RECORD. AL  |
| KIND                 | AL, AM, A CU, CA, CA, AM, A HU, ID, I LU, IV, M LU, IV, M LU, IV, M CH, IV, IV, M CE, CG, C AI AI CH, DB, D LIT, IV, F AI CH, BB, D LIT, IV, F AI CH, BB, D CH, BB, BB, D CH, BB, BB, BB, BB, BB, BB, BB, BB, BB, B  | ipitate c<br>ific tempo   |
| PATENT NO.           | WO 2003087039 W. AE, AG, A. C. CB, CB, GC, CB, GC, CB, CB, LT, IJ, PL, PL, PL, PL, PL, PL, PL, PL, PL, PL  | then to prected the drying at a spectage REFERENCE COUNT:   |

46 HCAPLUS COPYRIGHT 2007 ACS ON STN
2003.737716 HCAPLUS
139:230996
Preparation and properties of nateglinide salts
Sutton, Paul Allen, Vivilecchia, Richard Victor;
Parker, David John; De La Cruz, Marilyn
Novariis Ag, Switz.; Novartis Pharma Gmbh
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T: 1 L4 ANSWER 27 OF 46 H ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(\$): PATENT ASSIGNEE(S): SOURCE:

DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

20030310 CA, CH, CN, GD, GE, GH, IK, IT, IU, RO, RU, SC, YU, ZA, ZW DATE WO 2003076393 WE AE, AG, A CO, CR, C HR, HU, I LV, MA, WA, SE, SG, S PATENT NO.

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Page 93

10/507255 SALTS OF NATEGLINIDE - STR salt Search

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|  | DATE  20020716  BZ, CA, CH, CN, CN, CB, GD, GE, GH, NO, NZ, MY, TR, TT, TZ, CM, AM, AZ, BY, DE, DK, EE, ES, TK, EF, BY, CE, TG  20020715  P 20010716  W 20020716  4-(RIRZCH)C644C02H |
| CY, CY, PT, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20   | D CA, CA, GD, LC, TR, TR, TR, CA, CA, CA, CA, CA, CA, CA, CA, CA, CA   |
| BG, CH, CY, CZ, DE, MC, NL, PT, RO, SE, S59 20030310 200303030 2003030000000000  | BZ,<br>GB,<br>KZ,<br>NO,<br>TN,<br>TW,<br>TG,<br>TG,   |
| BG, CH, NC, NL, NC, NL, NC, NL, NC, NL, NC, NL, NL, NL, NL, NL, NL, NL, NL, NL, NL   | NN NO.  122631  127631  127631  127631  127631  127631  127631  127631   |
| 17, BE, 17, LU, 17, LU, 17, LU, 17, LU, 18, 23-24788 33-214113 3-5746 33-80-58 33-80   | TION NO<br>1022637<br>BK, BK, KK, KK, KK, KK, KK, KK, KK, KK,  |
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C1-8 (un)branched alkyl, cycloalkyl; e.g., 4-isopropylbenzoic acid] comprises oxidizing the corresponding aromatic aldehyde 4-(RIRZCH)CGH4CH0 (e.g., 4-isopropylbenzaldehyde) with a gas having an oxygen content of 1-100% at 20% to <100% in the presence of a supported Group VIII metal caralyst (e.g., Pt/C), and using a solvent having a flash point the solvent a m.p. <55% provided that the flash point of the solvent is greater than the reaction temperature

Synthesis process for trans-4isopropylcyclohexanecarboxylic acid
isopropylcyclohexanecarboxylic acid
isonorylicyclohexanecarboxylic acid
iluang, Zhishu
Zhongshan Univ., Peop. Rep. China
Eming Zhuanli Shenqing Gongkai Shuomingshu, 6 pp.
CODEN: CNXXEV HCAPLUS COPYRIGHT 2007 ACS on STN 2003:62632 HCAPLUS 138:73015 ANSWER 29 OF 46 PATENT ASSIGNEE (S): L4 ANSWER 29 OF ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S):

20010116 20010116 APPLICATION NO. CN 2001-107459 CN 2001-107459 20011031 DATE Patent Chinese KIND Ø COUNT: FAMILY ACC. NUM. CC PATENT INFORMATION: CN 1319583 PATENT NO.

The process comprises hydrogenating cumic acid in acetic acid in the presence of PtO2, recovering solvent, treating with 10-33% inorg, base (such as Ba(OH)2, Mg(OH)2, KOH, or NaOH) solution at 50-150° for 10-20 h, neutralizing with HCl to pH 2, crystallizing, filtering, and recrystg. in methanol. CASREACT 138:73015 PRIORITY APPLN. INFO.: OTHER SOURCE(S): AB The process compri

HCAPLUS COPYRIGHT 2007 ACS on STN 2003:30017 HCAPLUS 139:210299 ANSWER 30 OF 46 L4 ANSWER 30 OF ACCESSION NUMBER: DOCUMENT NUMBER: AUTHOR (S): TITLE:

Beijing Hospital, Ministry of Public Health, Beijing, 100730, Peop. Rep. China 2hongguo Yaoxue Zazhi (Beijing, China) (2002), 37(6), 444-446 Study on separation of cis-isomer of nateglinide by high-pressure liquid chromatographic method Yan, Xiaoyan; Hu, Xin; Cao, Guoying; He, Xiaorong; CODEN: ZYZAEU, ISSN: 1001-2494 CORPORATE SOURCE: SOURCE:

A high-pressure liquid chromatog. method for the separation of cis-isomer of nateglinide was established on Phenomenex Luna C18 column (5  $\mu m,$  4.6  $\mu m$  x 250  $\mu m$ ) with UV detection at 214 nm and room temperature. The mobile phase LANGUAGE: E S AB

Zhongguo Yaoxue Zazhishe

Journa

PUBLISHER: DOCUMENT TYPE:

consisted of (A) acetonitrile and (B) 0.03 mol L-1 phosphate buffer (pH 2.5, 65:35, volume/volume). The resolution factors were at least 1.5. The limits of detection and quantitation limit was 0.06 and 0.18  $\mu g$  mL-1, resp. The method is useful in separation and determination of the cis-isomer from

nateglinide

searched 5/2/07 Page 95

## 10/507255 SALTS OF NATEGLINIDE - STR salt Search

| ANTERNATION NUMBER:  100.000   | inide as antidiabetic Ping; Zhao, Yanfang ring, Shenyang ang, 110016, Peop. (2), 12(2), 94-96 (jibu from isopropylbenzene alyric hydrogenation ylation of  | linide crystals<br>Miyazaki, Kazuo;<br>iko   | DATE  20011023 BZ, CA, CH, CN, GB, GD, GE, CH, KX, LC, LK, LR, LR, LY, TZ, LC, LK, LR, LY, TZ, LC, LK, EF, SN, TD, TG SE, TR, BE, CH, CY, PT, SE, TR, BE, CH, CY, TD, TG SE, TR, BE, CH, CY, PT, SE, TR, EF, SN, TD, TG 20011023 20011023 20011023 20011023 20011023 20030424 A 20001024   |
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| 46 HCAPLUS CC 2002:69 138:2549 138:2549 138:2549 138:2549 138:2549 138:2549 128:2549 128:2549 128:2549 128:2549 128:2549 128:2549 138:2549 138:2549 138:2549 138:349 1 | a d a d a d a d a d a d a d a d a d a d  | M ateg<br>to;<br>Yub   | APPLICATION NO.  WO 2001-JP9293 BA, BB, BG, BR BY, BC, EC, EE, ES, FI, YW, MW, MW, MW, MW, MW, MW, MW, MW, MW, M   |
| LICA ANSWER 31 OF 46  DOCUMENT NUMBER: TITLE:  AUTHOR(S):  CORPORATE SOURCE:  SOURCE:  PUBLISHER: DOCUMENT TYPE: LANGUAGE:  AB A new antidiaber by Friedel-Craft to obtain trans D-Phenylalanine and crystal-con L4 ANSWER 32 OF 46 ACCESSION NUMBER: DOCUMENT TYPE: LANGUAGE: PATENT ASSIGNEE(S): SOURCE: WO 2002034713 W: AE, AG, EAMILY ACC. NUM. COU PATENT NOOMATION: PATENT NOOMATION PATENT NOOMATION: PATENT NOO | HCAPLUS COPYRIGHT 2002:609152 HC 138:254901 a new synthesis drug Wang, Dun; Lian School of Pharm Pharmaceutical Rep. China Zhongguo Yaowu CODEN: ZHYEEF; Zhongguo Yaowu CODEN: Zhongguo Yaowu CORN: Zhongguo Yaowu CORN: Zhongguo Yaowu CORN: Zhongguo Yaowu CONSEACT 138:25 Lic drug-nateglinide Ex reaction, chlorof Et ester, hydrolysiversion. The total | HCAPLUS COPYRIGHT 2002:332157 HC 136:340998 Process for pro Sumikawa, Michia, Mishina, Shigeh Ajinomcko Co., PCT Int. Appl., CODEN: PIXXD2 Patent Japanese   | KIND  1. AM, AT,  1. AM, AT,  1. U, ID, ID,  1. ID, ID,  2. II, IN,  3. II, IN,  1. IN |
|  | LIA ANSWER 31 OF 46 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: AUTHOR(S): CORPORATE SOURCE: SOURCE: DOCUMENT TYPE: LANGUAGE: OTHER SOURCE(S): OTHER SOURCE(S): AB A new antidiabe by Friedel-Craf to obtain trans D-Phenylalanine and crystal-con   | L4 ANSWER 32 OF 46 ACCESTON NUMBER: DOCUMENT NUMBER: INTLE: INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: LANGUAGE: FAMILY ACC. NUM. COUPENITY ACC. NUM. COUPENITY ACC. PATENITY ACC. PATENIT | ENT NO. 20020347 W. R. A. C. CO, CO, CO, ENT, ENT, ENT, ENT, ENT, ENT, ENT, ENT  |

no H-form crystals comprises the steps of drying wet crystals of a nateglinide solvate at a low temperature until the solvent disappears and then causing them to undergo a crystal transltion. Nateglinide is a known antidiabetic. By this process, B-form nateglinide crystals can be produced on an industrial scale.

REFERENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT A process for producing B-form nateglinide crystals containing substantially Process for producing nateglinide crystals
Takahashi, Daisuke; Nishi, Seiichi; Takahashi, Satoji
Ajinomoto Co., Inc., Japan
PCT Int. Appl., 14 pp.
CODEN: PIXXD2 HCAPLUS COPYRIGHT 2007 ACS on STN 2002:314896 HCAPLUS 136:325825 L4 ANSWER 33 OF 46 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE (S): INVENTOR (S): TITLE: B

Japanese Patent FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE: LANGUAGE:

SOURCE:

BE, CH, CY, SE, TR, BF, TD, TG 20011016 20011016 20011016 SE, MC, PT, CH, CN, CE, GH, LK, LR, PH, PL, UA, UG, 20011016 20011016 20011016 20011017 20030411 20030418 20001018 20011016 20011016 20011016 E 83 SL, SZ, TZ, UG, ZW, AT, B TE, IT, LU, MC, NL, PT, SI GQ, GW, ML, MR, NE, SN, TT AU 2001-94265 CA 2001-242538 EP 2001-974875 GB, GR, IT, LI, LU, NL, SI CY, AL, TR W 2003-111021 CY 2005-10118852 US 2003-418105 US 2003-418105 BZ, GB, KZ, NO, BR, BY, ES, FI, KP, KR, MX, MZ, TM, TR, WO 2001-JP9069 BB, BG, BK, BY, EC, EE, ES, FI, KE, KG, KP, KR, MN, MW, MX, MZ, SL, TJ, TM, TR, JP 2000-317604 CN 2001-820658 WO 2001-JP9069 APPLICATION NO. SK, YP, 20020425 AU, AZ, DK, DM, IN, IS, MD, MG, SG, SI, AU, AZ, DM, DM, DM, DM, MG, SG, SI, ZW, MZ, SD, GB, GR, GB, GR, GB, GR, CO030413 DK, ES, FR, 20031014 20031014 20060410 20060510 20060321 20050415 20050415 20070424 KIND AH, CZ, CZ, SD, YU, SD, YU, CI, CI, AH СС2 ВВ3 ВВ3 PRIORITY APPLN. INFO.: R: AT, BE, ( IE, SI, 1 ( 2001014729 BR 2001014729 RU 2273629 CN 1769263 TW 251588 . IN 2003GN00537 US 2004030182 US 7208622 AU 200194265 CA 2425538 EP 1334963 PATENT NO.

CASREACT 136:325825 OTHER SOURCE(S):

A process for producing nateglinide crystals comprises reacting trans-4-isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a mixed solvent consisting of a ketone solvent and water in the presence of an alkali to obtain a reaction mixture containing nateglinide, adding an acid

the reaction mixture to make it acidic, and regulating (a) the temperature to  $58^\circ$  to  $72^\circ$  and (b) and the ketone solvent concentration to > 8 weight\* and < 22 weight\*, to conduct crystallization Nateglinide is a known

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antidiabetic.

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The process is an industrially advantageous method for crystallizing

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 136:340997
Process for preparation of acylphenylalanines Sumikawa, Michito; Ohgane, Takao Ajinomoto Co., Inc., Japan PCT Int. Appl., 14 pp. CODEN: PIXXD2 2002:314895 HCAPLUS Japanese Patent HCAPLUS COUNT: L4 ANSWER 34 OF 46 ACCESSION NUMBER: PATENT ASSIGNEE(S): FAMILY ACC. NUM. CO nateglinide. REFERENCE COUNT: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR (S): LANGUAGE SOURCE:

20011016 CA, CH, CN, GD, GE, GH, LC, LK, LR, NZ, PH, PL, TZ, UA, UG, A 20001018 W 20011016 Al 20030418 CY, 20011016 20011016 20011016 SE, MC, PT, 20011016 20011016 20011017 20030411 20030418 20051228 GH, TR, BZ, KZ, TT, NĽ, ST, MU 2001-94264 MU 2001-94264 MU 2001-94874 GB, GR, IT, LI, LU, NI, AL, TR TR 2001-14728 NU 2003-111012 TW 2001-90125695 I TW 2001-90125695 IN 2003-418102 ZW, NE, US 2005-319177 JP 2000-317603 WO 2001-JP9068 US 2003-418102 APPLICATION NO. WO 2001-JP9068 BR, ES, KP, ÄŘ, 라 차 차 차 BG, KG, TJ, 72, H, U, A SE, KE, SZ, IT, GW, SK, YP, SE, H. SENERGE SE ; ; PRIORITY APPLN. INFO.: BR 2001011728 RU 2287520 TW 575541 IN 2003CN00536 US 2004024219 US 7030268 US 2006155143 R: AT, BE, IE, SI, AU 200194264 CA 2425533 EP 1334962 PATENT NO.

and simply high-purity This document discloses a process for preparing easily and simply high-puracybenylalanines extremely useful as raw materials of drugs or the like, characterized by reacting an acid chloride with phenylalanine in a mixed solvent consisting of an organic solvent and water under conditions made CASREACT 136:340997 OTHER SOURCE(S): ЯВ

alkaline

ALKALINI with potassium hydroxide. 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Drugs for diabetes, especially type 2, comprising L4 ANSWER 35 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2002:293592 HCAPLUS DOCUMENT NUMBER: 136:225420 TITLE: Drugs for diabetes accession:

an

antiinflammatory or analgesic drug, selected bivalent linkers, and a nitrate ester Del Soldato, Plero Nicox S.A., Fr. PCT Int. Appl., 66 pp. CODEN: PIXXD2 English Patent INVENTOR(S):
PATENT ASSIGNEE(S):
SOURCE: FAMILY ACC. NUM. CC PATENT INFORMATION: DOCUMENT TYPE: LANGUAGE

4): inhibition by 2 50% of DPPH-induced radical production in MeOH solution For instance, acetylsalicylic acid chloride was esterified with 3-(hydroxymethyl)phenol (80%), followed by nitation of the resultant Ph ester with HNO3/HZSO4 (82%), to give invention compound II, which is thus the 3-(nitrooxymethyl)phenyl ester of aspirin. When tested on isolated aorta from insulin-resistant rats, compound II at a concentration of 10-4 M

(test

gave

70% vasorelaxation, relative to non-insulin-resistant controls. This effect was unchanged by the presence or absence of the irreversible NO synthetase inhibitor LNNA. In contrast, both Na nitroprussiate and the indomethacin analog of II, known NO donors, were inactive, and the antidiabetic drug metformin was inactivated by LNNA.

ANSWER 36 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 5510N NUMBER: 2002:174779 HCAPLUS ENT NUMBER: 137:370326

L4 ANSWER 36 OF ACCESSION NUMBER: DOCUMENT NUMBER:

of bivalent linkers B and C, alone or in combination, are based on performance of the precursors of the linkers in certain tests (no data). These tests are designated as follows: (test 4A): inhibition by > 15% of hemolysis of rat erythrocytes induced by cumene hydroperoxide; (test 5): inhibition of radical production by z = 50% in the oxidative degradation of desoxyribose in aqueous Fe2+(NH4)2(SO4)2/thiobarbituric acid solution; and

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CZ, DM, DZ, IK, IR, LT, TR, TT, UA, TM EE, CH, CY, SE, TR, BF, TD, TG 20011009 20011009 20011009 20011009 20030411 20001012 SE, MC, PT, 20011009 , GB, GR, IT, LI, LU, NL, SI CY, AL, TR 5 JP 2002-53426 5 UZ 2003-39811 NO 2001-EP11665 W CU, IC, SK, SY, CR, KR, SI, RU, NL, NE, CA 2001-2425655 AU 2002-14006 EP 2001-982414 Z, TZ, UG, ZW, T, LU, MC, NL, W, ML, MR, NE, 2000-MI2201 APPLICATION NO. WO 2001-EP11665 SZ, IT, GW, IT 2 BR, IN, NZ, BY, SL, IE, ES, FR, RO, MK, 20020418 20020725 BB, BG, II, MX, NO, MX, NO, MA, NO, MA, SD, GB, GR, GA, GN, 20020412 20020412 20020412 20020418 H, H A, W, W, W, KIND A2 A3 AU, HR, MK, YU, CI, CI, A1 A1 A2 R: AT, BE, CH, I.
IE, SI, LT, L.
JP 2004511456
US 200407777 PRIORITY APPLN. INFO.: AE, AG, EE, GD, LV, MA, US, UZ, GH, GM, DE, DK, IT 2000MI2201 IT 1319201 CA 2425655 AU 200214006 EP 1324974 WO 2002030867 WO 2002030867 PATENT NO.

MARPAT 136:325420

OTHER SOURCE(S): GI

Useful for the treatment of diabetes, particularly type 2, are compds. or salts thereof, having the following general formula A-(Bn-(C)m-NO2 [I; wherein A = radical of a drup having an antinflammatory or analgesic activity; B = bivalent linking group wherein the precursor must meet certain tests described in the application; C = another defined bivalent linking group; n and m = 0 or 1, provided that (n + m) = 1 or 2]. I can be used in conjunction with other antidiabetic drugs, particularly insulin. I increase the direct antidiabetic effect of insulin, and reduce complications of diabetes, particularly vascular diseases, retinopathies, neuropathies, etc.. The values of n and m, i.e., the presence or absence ΑB

searched 5/2/07

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Synthesis of [14C]- and [3H]DJN608 [STARLIX]
Ray, T.; Ciszewska, G.; Mu, A.; Jones, L.
DMFK-Isotope Section, Novartis Pharmaceuticals, E.
Hanover, NJ, USA
Synthesis and Applications of Isotopically Labelled
Compounds, Proceedings of the International Symposium,
7th, Dresden, Germany, June 18-22, 2000 (2001),
Meting Date 2000, 228-231. Editor(s): Pleiss,
Ulrich: Voges, Rolf. John Wiley & Sons Ltd.:
Chichester, UK.
CODEN: 69CIJC; ISBN: 0-471-49501-8 AUTHOR(S): CORPORATE SOURCE:

Conference DOCUMENT TYPE:

CASREACT 137:370326

A novel oral medication for treating type 2 diabetes is trans-N-[(4-(1-methylethyl)cyclohexyl)]-carbonyl]-D-phenylalanine, DN608 (Starlix). The key step in the synthesis of [14(c]DN608 was the catalytic reduction of [carboxy-14c]cumic acid in the presence of PrO2 at 55 psi of hydrogen in acetic acid to give cis/trans-4-isopropylcyclohexane-[14(c]carboxylic acid in 3:1 ratio. Alternatively methods for preparing this mixture of cis- and trans- acids (3:1) are presented. Tritiated DN608 was prepared by reduction of the corresponding chloro derivative with tritium gas OTHER SOURCE(S):

in the presence of 10% palladium on carbon.

REFERENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT in the

ANSWER 37 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN 2002:130037 HCAPLUS 137:325603 L4 ANSWER 37 OF ACCESSION NUMBER: DOCUMENT NUMBER:

Zhu, Xue-yan; Peng, Ka; Wang, Xiao-qin; Yang, Li-ping Dep. Chem., East China Normal Univ., Shanghai, 200062, Peop. Rep. China Hecheng Huaxue (2001), 9(6), 537-540 CODEN: HEHUEZ; ISSN: 1005-1511 Synthesis of Nateglinide AUTHOR(S): CORPORATE SOURCE:

Hecheng Huaxue Bianjibu CASREACT 137:325603 OTHER SOURCE(S): DOCUMENT TYPE: LANGUAGE: PUBLISHER: æ

Title compound, a new antidiabetes medicine, was synthesized from iso-propylbenzene in seven steps, giving the product with overall yield Title compound,

derivatives as cysteine protease inhibitors
Sato, Masaaki; Mukoyama, Harunbou Kobayashi, Junichi;
Sato, Kissaaki; Mkokoyama, Harunbou Kobayashi, Junichi;
Kissei Pharmaceutical Co., Itd., Japan
Jpn. Rokai Tokkyo Koho, 27 pp. Preparation and effect of cycloalkylcarboxamide APPLICATION NO. HCAPLUS COPYRIGHT 2007 ACS on STN 2001:38482 HCAPLUS 134:100592 DATE Japanese Patent KIND COUNT: ANSWER 38 OF 46 PATENT ASSIGNEE(S): FAMILY ACC. NUM. CC PATENT INFORMATION: L4 ANSWER 38 OF ACCESSION NUMBER: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR (S): LANGUAGE:

19990701 JP 1999-188275 JP 1999-188275 MARPAT 134:100592 20010116 æ PRIORITY APPLN. INFO.: OTHER SOURCE(S): GI JP 2001011037

CONH-CH-CO-COZR3

Title compds. [I: R1 = alkyl: Y = alkylene; R2 = OH, aryl, aryl alkoxy; R3 = H, alkyl, aryl, pyridyl, arylalkyl, pyridylalkyl; Z = O, NH; D = 1 integer 1-3] and stereoisomers are prepared and possesses the cysteine protease Æ

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inhibitory effect. Title compds. are useful in prevention of arthritis, Alzheimer's disease, rheumatism and osteoporosis. Thus, the title compound II was prepared and tested.

Hybridization of non-sulfonylurea insulin secretagogue and thiazolidinedione-derived insulin sensitizer Kitajima, Hiroshi; Nakamura, Mitsuharu; Tamakawa, Hiroki; Goto, Nobuharu Baratment of Dascovery Research, Welfide Corporation, Hirakata, 573-1153, Japan Bioorganic & Medicinal Chemistry Letters (2000), 10(21), 2453-456 CODEN: BMLES; ISSN: 0960-894X L4 ANSWER 39 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACESSION NUMBER: 2000:840649 HCAPLUS DOCUMENT NUMBER: 134:110109 Journal CORPORATE SOURCE: DOCUMENT TYPE: LANGUAGE: GI AUTHOR(S): PUBLISHER: SOURCE: TITLE:

L4 ANSWER 40 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1997:228845 HCAPLUS DOCUMENT NUMBER: 126:220267

Structure determination of metabolites isolated form urine and bile after administration of AV4166, a novel D-phenylalanine-derivative hypoglycemic agent.

[Erratum to document cited in CA126:325]
Takesada, Hiroko; Matsuda, Keizo; Ohtake, Ryoko; Mahaza, Ryuichi; Ono, Ichiro; Tanaka, Kenzo; Naito, Masski; Yataqai, Masanobu; Suzuki, El-Ichiro Central Research Laboratories, Ajinomoto Co., Inc., CORPORATE SOURCE: AUTHOR (S):

Kawasaki, 210, Japan Bloorganic & Medicinal Chemistry (1997), 5(3), 637 CODEN: BMECEP, ISSN: 0968-0896 PUBLISHER: DOCUMENT TYPE: SOURCE:

Elsevier

DAGE:
On page 1771 (column 2, line 26) and 1772 (column 1, line 2), the functional group of M2 in Figure 1, which was converted from one of two methyl groups of AY4166, should read hydroxylmethyl instead of methoxyl. On page 1776, column 2, in the parentheses of the fourth line from last, 60 mg/kg should read 60 mg/man. LANGUAGE:

Structure determination of metabolites isolated from urine and bile after administration of AY166, a novel D-phenylalanine-derivative hypoglycemic agent Takesada Hiroko; Matsuda, Keizo; Ohtake, Ryoko; Mihza, Ryuichi; Ono, Ichiro; Tanaka, Kenzo; Naito, Maski; Yatagai, Masanobu; Suzuki, Ei-ichiro; Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, 210, Japan
Bioorganic & Medicinal Chemistry (1996), 4(10), HCAPLUS COPYRIGHT 2007 ACS on STN 1996:702133 HCAPLUS CODEN: BMECEP; ISSN: 0968-0896 Elsevier 126:325 English 14 ANSWER 41 OF 46 ACCESSION NUMBER: DOCUMENT NUMBER: CORPORATE SOURCE: DOCUMENT TYPE: AUTHOR(S): LANGUAGE: AB Mol. PUBLISHER: SOURCE:

AB Mol. structures of 10 metabolites, which were isolated from urine (M1-M8) or bile (M9 and M10) after administration of AY4166 (N-(trans-4-isopropylyclohexanecarbonyl)-D-phenylalanine), with hypoglycemic activity, were elucidated by mass spectrometry and NRR. Four of these (M1, M2, M3 and M8) were hydroxyl derivs. of AY4166, 2 (M9 and M10) were carboxylate derivs. via oxidation of M2 and M3, 3 (M4, M5 and M6) were glucuronic acid conjugates and the other (M7) was a dehydro derivative fructures for M1, M2, M3, M7, M8, M9 and M10 were confirmed by the coincidence of the retention time of HPLC, MS and IH-MR spectra between the isolated metabolites and authentic synthesized substances. For 3 qlucuronic acid conjugates, M4, M5 and M6, structural confirmation was performed by a selective enzymic digestion with \$P-qlucuronidase. M1 m3 and M2/3 were about 5-6 and 3-fold less potent than AY4166, resp., and M7 was almost as potent as AY4166.

Preparation of trans-4-isopropylcyclohexanecarboxylic acid chloride Matsuzawa, Toshihiro; Irie, Yasuo Ajinometo KK, Japan Jpn. Kokai Tokkyo Koho, 3 pp. CODEN: JKXXAF HCAPLUS COPYRIGHT 2007 ACS on STN 1995:468819 HCAPLUS Japanese LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: ANSWER 42 OF 46 INVENTOR(S): PATENT ASSIGNEE(S): L4 ANSWER 42 OF ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: SOURCE:

19930701 19930701 DATE APPLICATION NO. JP 1993-163426 JP 1993-163426 19950120 DATE KIND Ą PRIORITY APPLN. INFO.: OTHER SOURCE(S): JP 07017899 PATENT NO.

ROURCE(S): CASREACT 123:55430
The title compound (I), useful as an intermediate for antidiabetic

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treatment of trans-4-isoptopytoyclohexanecarboxylic acid (II) with P chloride. II was treated with PCI5 in 1,2-dichlorocthane at 40° for 3 h to give 94% I and 0% the cis-isomer, whereas cis-isomer was detected, when SOC12 was used instead of PCI5.

Stable crystals of N-(trans-4-lsopropy/cyclohexy/carbonyl-0-phenylalanine Sumkawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji ANSWER 43 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN SSION NUMBER: 1993:261002 HCAPLUS Ajinomoto Co., Inc., Japan Eur. Pat. Appl., 14 pp. CODEN: EPXXDW Patent 118:261002 English COUNT: PATENT ASSIGNEE (S): FAMILY ACC. NUM. CC PATENT INFORMATION: L4 ANSWER 43 OF ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): LANGUAGE: SOURCE:

19920729 19920729 19920729 19920729 A 19910730 AT 1992-306895 ES 1992-306895 CA 1994-2114678 IT, LI, LU, NL, SE JP 1992-202686 APPLICATION NO. JP 1991-189696 JP 1991-199453 EP 1992-306895 19970616 19950802 19990427 FR, GB, 19930820 19930203 19930505 19960619 19970315 DATE DK, ES, KIND A2 A3 C 113 CH, DE, PRIORITY APPLN. INFO.: R: AT, JP 05208943 JP 2508949 AT 149483 ES 2100291 CA 2114678 CA 2114678 EP 526171 EP 526171 EP 526171 PATENT NO.

Stable H-type crystals of N-(trans-4-isopropylcyclohexylcarbony)-D-phenylalanine (1) are obtained by treating I with a solvent, at >10°. A solution of 5 g I in 20 mL acetone was added to a stirred mixture of 40 mL acetone and 60 mL water, at 25° to precipitate H-type crystals. The crystals have different m.p., IR spectrum and x-ray differents from known forms of I and are not converted to other forms when ground.

Shinkai, Hisashi; Nishikawa, Masahiko; Sato, Yusuke; Toi, Koji; Kumashiro, Izumi; Seto, Yoshiko; Fukuma, Artico; Dan, Katsuaki; Toyoshima, Shigeshi Cent. Res. Lab., Ajinomoto Co., Inc., Kawasaki, 210, N-(Cyclohexylcarbonyl)-D-phenylalanines and related compounds. A new class of oral hypoglycemic agents. L4 ANSWER 44 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1989;458305 HCAPLUS DOCUMENT NUMBER: 111:58305 CORPORATE SOURCE: AUTHOR(S):

Journal of Medicinal Chemistry (1989), 32(7), 1436-41 CODEN: JMCMAR; ISSN: 0022-2623 Journal Japan DOCUMENT TYPE: LANGUAGE: SOURCE:

CASREACT 111:58305

OTHER SOURCE(S):

ij

and A series of analogs, e.g., I (R = alkyl, Ph), of N-(cyclohexylcarbonyl)-D-phenylalanine have been synthesized and evaluated for their hypoglycemic activity. Relationships were studied between the activity and the three-dimensional structure of the acyl moiety, which was characterized by high-resolution 1H NMR spectroscopy and MNDO calcns. The role of the carboxyl group of the phenylalanine moiety was also studied by comparing the activities of the enantiomers, the decarboxyl derivative, the esters, and the amides of the phenylalanine derivs. Thus, the structural requirements for possessing hypoglycemic activity was elucidated and a highly active compound, W-(Itrans-4-isoproplyclohexyl)carbonyl)-D-phenylalanine (I, R = CHMe2) was obtained, which showed a 20% blood glucose decrease at an oral Æ

use as hypoglycemic agents
Toyoshima, Shigeshi; Seto, Yoshiko; Shinkai, Hisashi;
Toyoshima, Shigeshi; Seto, Yoshiko; Shinkai, Hisashi;
Toi, Koji; Kumashiro, Izumi
Ajinomoto Co., Inc., Japan
CUE., Pat. Appl., 25 pp. Preparation of D-phenylalanine derivatives and their L4 ANSWER 45 OF 46 HCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 1987:85057 HCAPLUS Correction of: 1987:19047 Correction of: 106:19047 106:85057 DOCUMENT NUMBER: INVENTOR (S): TITLE:

PATENT ASSIGNEE(S): SOURCE:

English COUNT: LANGUAGE: FAMILY ACC. NUM. CC PATENT INFORMATION: DOCUMENT TYPE:

19860326 19860319 APPLICATION NO. EP 1986-302217 JP 1986-61833 19880224 19920129 19880308 19920317 19890328 19950314 19861001 П KIND A2 B1 B1 B A R: CH, DE, FR, G.
JP 63054321 A
JP 04015221 B
US 4816484 PRIORITY APPLN. INFO.: PATENT NO. EP 196222 EP 196222 EP 196222

US 34878
US 1986-6275
US 1986-844970
US 1986-844970
US 1988-146719
US 1988-14770
US 1988-1477 OTHER SOURCE(S): æ

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be converted thereto in the human or animal body, useful as hypoglycemics, were prepared via conventional N-acylating reactions. D-Phenylalanine in 10% aqueous NOHW was successively treated with Me2CO, 4-EtcGH4COCl in Me2CO, and 10% aqueous NOHL to give 83% acylphenylanine D-II. At 25 mg/kg in mice, D-II decreased blood glucose 34% in min.

use as hypoglycemic agents
Toyoshima, Shigeshi; Seco, Yoshiko; Shinkai, Hisashi;
Toi, Koji; Kumashiro, Izumi
Ajinomoto Co., Inc., Japan
Eur. Pat., Appl., 25 pp. Preparation of D-phenylalanine derivatives and their 19860326 19850327 APPLICATION NO. EP 1986-302217 ANSWER 46 OF 46 HCAPIUS COPYRIGHT 2007 ACS on STN ISION NUMBER: 1987:19047 HCAPIUS ENT NUMBER: 106:19047 JP 1985-62276 19861001 DATE English Patent KIND GB, LI R: CH, DE, FR, GE PRIORITY APPLN. INFO.: GI PATENT ASSIGNEE (S): PATENT INFORMATION: EP 196222 A2 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR (S): LANGUAGE: TITLE:

- CONHCHCH2Ph

H

D-Phenylalanine derivs. D-R2CONR3CH(COZRI)CH2Ph [I; R1 = H, C1-5 alkyl, C6-12 aryl or aralkyl, Q, CH2COZR3, CHMeCOR3, CH2COCCMe3; R2'= (un)substituted G6-12 aryl, 5- or 6-membered heterocyclyl, cycloalkyl, cycloalkyl, cycloalkyl, R3 = H, C1-5 alkyl), their salts, and precursors which can be converted thereto in the human or animal body, useful as hypoglycemics, were prepared via conventional N-acylating reactions. D-Renylalanine in 10% aqueous NaOH was successively treated with Me2CO, 4-Etc6H4COCl in Me2CO, D-II decreased blood glucose 31% in 60 min. ΑB